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HODGKIN'S DISEASE*

III. Symptoms and Course

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IN THE present installment of this series of papers on Hodgkin's disease, the initial symptoms of the three types of that condition will be discussed, and the general course of the disease will be briefly illustrated. In a subsequent issue, the symptoms and signs arising from involvement of certain organs will be discussed in more detail.

Hodgkin's Paragranuloma

Hodgkin's paragranuloma is a comparatively benign condition the onset of which is virtually always heralded solely by painless lymphadenopathy, usually in the cervical region (Table 1).

Systemic symptoms are absent at first, and the patient appears to be in good health. Occasionally the disease is discovered on routine physical examination.

According to our experience, approximately 20 per cent of the cases progress after months or years to Hodgkin's granuloma. It must be emphasized that the insidiousness of the onset in no way precludes this development and as we have already pointed out, those cases that progress cannot, even by the most careful histologic study, be distinguished in their incipiency from those that do not.

TABLE 1. *Initial Symptoms of Hodgkin's Paragranuloma (28 cases).*

SYMPTOMS	NO. OF CASES
Painless nodes in neck	23
Painless nodes in groin	2
Painless nodes in axilla	1
No symptoms	2

The course of Hodgkin's paragranuloma is extremely variable. In certain cases, there develop signs or symptoms suggesting a transition to Hodgkin's granuloma and death ensues within a short time; in others, many months or several years elapse before the development of Hodgkin's granuloma; in still others, the condition remains quiescent for many years, and death may be due to some intercurrent disease or the patient may survive and remain in excellent health for many years. In these last cases, however, there is always the possibility that the disease will once more become active or that Hodgkin's granuloma will develop. This has been seen to happen as long as nineteen years after the initial lesion was discovered. Involvement of the mediastinal lymph nodes may take place; this does not necessarily imply that Hodgkin's granuloma is developing, but enlargement of the spleen has, in our experience, been an ominous sign. The onset of systemic symptoms, such as fever, weakness, anorexia or loss of weight almost always indicates that a transition to the granulomatous form has taken place. There is no characteristic blood picture, although one occasionally finds an increased percentage of polymorphonuclear neutrophils. There is no anemia.

The following case histories illustrate the course of the disease.

CASE 1. J. H. (Pv. 5-42), a 40-year-old man, was first seen on May 20, 1942. Six years previously, he had noted a lump in the left groin. This did not bother him, and it remained approximately the same size until September, 1941, when it began to increase in size. It was therefore removed, and showed the typical features of Hodgkin's paragranuloma. There was also a small lymph node in the right axilla. Otherwise the physical examination was within normal limits. The blood picture was normal. A moderate amount of x-ray therapy was given to the left groin and to the node in the axilla.

The patient remained well until September, 1942, when he noticed some pain in the right upper quadrant of the abdomen and increasing weakness necessitating his resting when he returned home from work. At that time, there were a few small lymph nodes in both sides of the neck and in each groin. The spleen was palpable 4 cm. below the costal margin. Otherwise the physical examination revealed no notable abnormalities. The red-cell count was normal, but the white-cell count had risen to 20,000, with 80 per cent polymorphonuclear neutrophils. A moderate amount of x-ray therapy was given to each quadrant of the abdomen,

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and the patient improved considerably and gained weight. Nevertheless, a month later he again began to feel poorly and noted an elevation of temperature each afternoon. He was readmitted to the hospital and was found to have generalized lymphadenopathy. The red-cell count had fallen to 3,900,000, and he was therefore given several transfusions of whole blood. The x-ray examination of the chest showed numerous small patches of consolidation the nature of which was somewhat uncertain, although it was believed that since several of them were definitely nodular, the lesions probably represented metastases from a newly developed Hodgkin's granuloma. This suspicion seemed to be substantiated by the fact that the pulmonary lesions cleared up after an x-ray dosage of 1600 r had been given to the chest. X-ray therapy was then directed to the peripheral lymph nodes. The patient's general condition, however, did not improve. The fever continued, and he began to have drenching night sweats.

In January, 1943, generalized lymphadenopathy appeared. The red-cell count gradually fell to 1,600,000 and the hemoglobin to 35 per cent. Following further x-ray therapy and several blood transfusions, the patient improved somewhat and the fever subsided. After a very short time, however, the weakness and fever returned and the patient grew steadily worse until his death on March 20, 1943.

Autopsy showed widespread involvement by typical Hodgkin's granuloma.

This case illustrates the rapidity with which Hodgkin's paragranuloma occasionally develops into Hodgkin's granuloma.

CASE 2. F. S. (Pv. 8-29), a 45-year-old man, in 1927 first noticed a few small, painless lymph nodes beneath the right sternomastoid muscle. In 1929, a node was removed that on subsequent review showed the typical picture of Hodgkin's paragranuloma. There were no general symptoms at that time, the patient felt perfectly well, and no other abnormalities were noted on physical examination. X-ray treatment was given to the right cervical area, and the patient remained entirely asymptomatic for 6 years, — March, 1935, — when enlarged lymph nodes were noted in the left side of the neck. These were excised and showed a histologic picture suggesting a transition between Hodgkin's paragranuloma and Hodgkin's granuloma. X-ray therapy was again given, the lymph nodes subsided, and the patient remained asymptomatic until March, 1938. At that time, he developed a moderate degree of anorexia and definite bitemporal hemianopsia. He became weak, listless and apathetic. Physical examination was essentially normal except that the visual fields were notably contracted and the spleen could be felt 3 cm. below the costal margin. He was given an x-ray dosage of 600 r at 250 kv. to each side of the head, and his symptoms entirely subsided.

In June, 1938, the anorexia returned. In addition, the patient, a highly intelligent man of robust stature, noticed that all food tasted unusually sweet. With the passage of time, this sense of sweetness became so great that the patient, although co-operative, was unable to eat anything except the most highly spiced foods, and but little of these. A large mediastinal mass was visualized by x-ray, and a moderate degree of hypochromic anemia had developed. The white-cell count, normal at all previous examinations, had risen to 17,000, with 85 per cent polymorphonuclear neutrophils. The patient was given an x-ray dosage of 1000 r at 100 kv. to the head, with some temporary relief from the sensation of sweetness. The mediastinal mass completely disappeared after 800 r to the anterior part of the chest. The anorexia, however, became increasingly severe, and for the next 6 months the patient subsisted almost entirely on peptonized milk and hard-boiled eggs, to each of which he added, in order that they might not "taste too sweet," astounding amounts of cayenne pepper. There was no suggestion of hysteria, and all those who examined him were convinced that the symptoms had an organic basis, although no one was able to localize the lesion. He became extremely emaciated, as might well be expected, and died on April 27, 1939, 10 years after the onset of his condition.

Autopsy failed to reveal, even after the most careful and scrupulous examination, any lesion, either gross or microscopic, in the nervous system to account for the hemianopsia or the abnormality of taste. A few enlarged lymph nodes, particularly about the head of the pancreas and in the retroperitoneal area, showed the histologic changes of Hodgkin's granuloma. The most prominent lesion seen was an extreme degree of amyloidosis, chiefly in the lymph nodes, kidneys, liver and spleen. Although Hodgkin's granuloma was found at autopsy, the lesions were not extensive enough to cause death, which must be attributed to inanition following extreme anorexia, the cause of which remains entirely obscure.

CASE 3. J. H. (B. C. H. 408240), a 17-year-old man, was admitted to the hospital on September 22, 1920, with the sole complaint of painless lymph nodes in the right side of the neck. The past history had been uneventful. In 1915, he noted a few small lymph nodes in the right side of the neck. These increased slowly in size, and in 1917 one was removed for diagnosis. No record of this biopsy had been preserved. In August, 1920, the patient complained of an increasing sense of constriction in the neck and upper thorax and noticed that the lymph nodes in the cervical region had increased greatly in size.

Physical examination at that time revealed no abnormalities except for the presence of a large number of firm, elastic nodes in the right side of the neck, extending from the mastoid region to the supraclavicular area. A radical dissection was done and all the apparently diseased tissue was removed. Examination of the lymph nodes showed the typical picture of what we now recognize as Hodgkin's paragranuloma. Unfortunately, the patient was told by one of his friends that he would die in 6 months, and as a respite from this gloomy outlook, he had recourse to hard liquor in large amounts. At the end of a year, he was still alive but was unable to forego alcohol. He remained symptom-free, however, until September, 1939, when he again noticed nodes above the clavicle and a sense of tightness in the neck. Physical examination showed many firm nodes above the right clavicle; these appeared to extend into the thoracic cage. A biopsy showed that the process had progressed into a typical Hodgkin's granuloma. A large mediastinal mass developed, and in spite of x-ray therapy, the patient died in 1942, 27 years after the initial lymphadenopathy and 3 years after the known transition of the Hodgkin's paragranuloma into Hodgkin's granuloma.

CASE 4. L. C. (Pv. 2-36), a 36-year-old woman, was admitted to the hospital in April, 1936. In 1910, at the age of 10 years, enlarged lymph nodes had appeared in the right side of the neck. These had been removed at another hospital and showed the histologic picture of what we now call Hodgkin's paragranuloma. The patient remained entirely well until 1917, when the nodes recurred. They were removed and again showed precisely the same features as they had in 1910.

No further signs or symptoms occurred until February, 1936, when masses were once more noted in the right side of the neck. Physical examination showed no abnormalities except that beneath the upper third of the right sternomastoid muscle were a group of firm, freely movable nodes. These were excised as completely as possible, and they too showed the histologic features of Hodgkin's paragranuloma. Thus there had been no appreciable change in the histologic picture since 1910. At present, 34 years after the initial lymphadenopathy, the patient is free of signs and symptoms.

This case illustrates the benign character of the process when it remains unaltered. Why one patient rapidly develops Hodgkin's granuloma whereas another remains in comparatively good health is entirely obscure.

HODGKIN'S GRANULOMA

It is of the greatest importance to recognize clearly the extraordinarily protean character of the symptomatology of Hodgkin's granuloma. It is true that in the majority of cases painless enlargement of one or more cervical lymph nodes first attracts the patient's attention to his condition, yet so diverse are the symptoms and so varied are the signs that almost any disease may be simulated

and any system may appear to be primarily implicated.

Initial Symptoms

As will be seen from Table 2, painless enlargement of cervical lymph nodes is by far the most frequent initial symptom of the disease. They may be situated in the anterior or posterior triangles or under the sternomastoid muscle. Not infrequently an upper respiratory infection has immediately preceded the enlargement, which may diminish greatly with the subsequent subsidence of the acute process, so that the physician is not unnaturally led to suppose that he is dealing with a simple inflammatory lymphadenopathy and treats the case accordingly. In other cases, a varying though moderate degree of lymphadenopathy is present over a considerable period of time, and increases after a respiratory infection to such a degree as to demand medical attention. This sequence of events is seen in the following case.

TABLE 2. *Initial Symptoms of Hodgkin's Granuloma (213 cases).*

SYMPTOMS	NO. OF CASES
Enlarged cervical lymph nodes	111
Pain (usually in abdomen or back)	26
Weakness	14
Enlarged axillary lymph nodes	14
Enlarged inguinal lymph nodes, anorexia, cough	9 each
Dyspnea, loss of weight, abdominal mass	7 each
Chills	5
Itching	4
Vomiting	3
Weakness of legs, amenorrhea, fever, hematemesis, edema of legs, hemoptysis	2 each
Melena, sternal mass, dysuria, enlargement of tonsil, sore throat, skin nodules, constipation, deafness, dysphagia, cyanosis, sweats	1 each

CASE 5. R. E. S. (P. H. 13671), a 24-year-old woman, was admitted to the hospital on March 10, 1938. In the spring of 1933, she had noticed enlarged, painless, nontender lymph nodes in the left side of the neck. There was no associated sore throat or upper respiratory infection, nor were there any constitutional symptoms. For the next 5 years, the nodes fluctuated in size for no ascertainable reason, varying from 1 to 2 cm. in diameter. Occasionally they disappeared entirely. There were no constitutional symptoms. In January, 1938, the patient developed an acute upper respiratory infection of considerable severity, and immediately thereafter the cervical nodes increased rapidly in size.

On entry to the hospital, physical examination revealed an obese, healthy-looking woman. In the anterior and posterior triangles of the left side of the neck and beneath the sternomastoid muscle were several firm, nontender lymph nodes varying from 2 to 5 cm. in diameter. There was no other lymphadenopathy, but the upper part of the mediastinal shadow was definitely widened in the x-ray film. Aside from a moderate elevation of the white-cell count and an increase of the percentage of polymorphonuclear neutrophils in the peripheral blood, the laboratory findings were within normal limits. A biopsy of one of the cervical lymph nodes showed Hodgkin's granuloma. Appropriate x-ray therapy was directed to the neck and mediastinum, with complete disappearance of all masses. The patient was still in excellent condition and gaining weight when last seen in May, 1944.

In a adult, the persistence of notably enlarged lymph nodes for a considerable period of time after an acute upper respiratory infection or the development of persistent masses in the neck after minor infections must be regarded with suspicion, particularly if the posterior triangle or the supraclavicular region is involved. Painless enlargement of lymph nodes in the neck unassociated with obvious infection always calls for careful investigation, and it has been our experience that without biopsy an accurate and definitive diagnosis cannot be made.

The enlarged lymph nodes are usually nontender, and rarely cause pain unless they press on adjacent nerves or are adjacent to obvious septic foci. Later, pain due to lymphadenopathy is more frequent, particularly when the lymph nodes are in the groin or the axilla. The overlying skin is usually normal in appearance, and the nodes are seldom fixed to the surrounding structures, although they may become immobile by the very fact that they fill the entire neck and impinge on contiguous fixed structures. It should be borne in mind, however, that as a result of poulticing or other self-medication, the overlying skin may become reddened and that an associated infection in the nasopharynx may cause the nodes to be temporarily painful and tender, even in the early stages of the disease. In consistence, the nodes are usually firm and rubbery, occasionally soft and rarely hard. They never have the stony feel so suggestive of metastatic carcinoma, unless they have already been subjected to heavy radiation. On rare occasions, the nodes are extremely soft and even fluctuant.

In our experience, there is no predilection for one or another side of the neck, and in the majority of cases, the involvement is bilateral when the patient is first seen, although almost invariably one side is involved to a far greater extent than the other, and only rarely does one see the evenly distributed bilateral nodes of uniform size and relatively soft consistence so often found in lymphatic leukemia. No particular part of the cervical region appears to be most frequently involved. It is wise, however, to search with special care for nodes beneath the sternomastoid muscles and in the region immediately above the clavicles. Enlarged nodes are not infrequently found in the submaxillary and submental regions, but those confined sharply to such regions are rarely due to Hodgkin's granuloma and are likelier to be secondary to some obscure infection of the floor of the mouth. This fact may be of some practical value in diagnosis.

Enlarged lymph nodes elsewhere, as in the axilla, groin and inguinal regions, have in general the same characteristics as those in the neck, although they are more prone to be painful and only rarely fluctuate in size, probably owing to the fact that they are less likely to be influenced by adjacent infectious processes.

Pain is the next most frequent initial complaint, but it should be emphasized that early in the course of Hodgkin's granuloma this symptom is compar-

atively rare. In Hodgkin's sarcoma and reticulum-cell sarcoma, on the other hand, pain is often an early and almost constantly a late symptom. The most frequent sites of pain are the abdomen and the back. In the former, it is in most cases caused by retroperitoneal lymph nodes, and it is perhaps surprising that this symptom is not found oftener, for many authors have emphasized the frequency with which the retroperitoneal nodes are involved, and our own experience is in agreement with this finding.

Only rarely is pain due to invasion of one of the abdominal viscera as in the following case.

CASE 6. E. M. (B. C. H. 559573), a 47-year-old man, was admitted to the hospital on May 10, 1923, with a chief complaint of upper abdominal pain. Thirteen years previously, he had been operated on for a "perforated gastric ulcer." No data were available as to the nature of this ulcer. Convalescence, however, had been uneventful, and the patient remained symptom-free until January, 1923, at which time he began to suffer from a burning epigastric pain occurring shortly after meals and lasting approximately an hour. There was no nausea or vomiting. During the next 3 months, he lost about 15 pounds, and 3 days before entry to the hospital he vomited "a cupful" of bright-red blood.

Physical examination on admission showed evidence of an old healed tuberculous process in the apex of the right lung and a moderate degree of anemia. The abdomen showed no tenderness, spasm or masses. X-ray examination revealed an extensive irregularity and mottling of the cardia and media of the stomach, and a diagnosis of carcinoma was made. The red-cell count was 3,280,000, the hemoglobin 55 per cent (Sahli) and the white-cell count 16,000, with 86 per cent polymorphonuclear neutrophils, 10 per cent lymphocytes and 4 per cent monocytes. The stools gave a strongly positive guaiac test. The patient failed rapidly, and in spite of two blood transfusions, the red-cell count fell to 2,800,000 and the hemoglobin to 40 per cent. Persistent vomiting developed, and he died 3 weeks after entry.

Autopsy showed extensive Hodgkin's granuloma of the stomach, with extension into the liver and pancreas and involvement of the gastric and retroperitoneal lymph nodes.

Rarely abdominal pain is caused by great enlargement of the spleen.

Pain in the back, usually in the lower thoracic or lumbar region, may be due to a variety of causes. In obscure cases, one is often forced to the conclusion that enlarged lymph nodes are pressing on one or more spinal nerves. Not infrequently back pain is due to direct involvement of the bodies of the vertebras or to granulomatous lesions in the dura or epidural space, and it is of the greatest importance to recognize the fact that lesions of the spine may be present for several months before they can be visualized on x-ray films. Pain due to involvement of bone is well illustrated by the following case.

CASE 7. B. B. (H. H. 36-543), a 34-year-old woman, was admitted to the hospital on May 25, 1936. In February, 1933, she began to complain of fleeting pains of no great severity in the low lumbar region. The pain was made worse by exercise, and was not constant. A careful physical examination at that time by her physician revealed only slight tenderness and spasm of the muscles in the right lumbosacral region. The symptoms continued with exacerbations and remissions, in spite of baking, massage and simple orthopedic measures, until May, 1935. The pain then became constant, was much worse at night and radiated from the lumbar region bilaterally to the lower abdomen. Nine months later, in February, 1936, the patient began to lose weight and to complain of anorexia, nausea and occasional attacks of vomiting.

Except for evident loss of weight, — she had lost 29 pounds, — the physical examination showed only a few discrete, firm, bean-sized lymph nodes in each side of the neck. The red-cell count was 3,890,000, the hemoglobin 63 per cent (Sahli), and the white-cell count 33,000, with 90 per cent polymorphonuclear neutrophils and 10 per cent lymphocytes. X-ray films of the spine and pelvis showed extensive hyperplastic changes in the bodies of the 3rd, 4th and 5th lumbar vertebras and in the left portion of the pelvis consistent with those of Hodgkin's granuloma. A biopsy of a small node in the right side of the neck showed the typical picture of that condition. X-ray therapy relieved the back pain for a few months, but splenomegaly, hepatomegaly and a left-sided pleural effusion developed, and the patient died in early October, 1937, 19 months after the bone lesion had been demonstrated by x-ray.

When the change from Hodgkin's paragranuloma to Hodgkin's granuloma actually first developed is of course, problematical, but this case illustrates the importance of careful x-ray studies in patients with obscure and recalcitrant back pain, and the wisdom of searching for enlarged lymph nodes that may give a clue as to the true condition.

Pain in the chest, shoulder, groin, leg or axilla is occasionally encountered as an initial symptom. Usually under such circumstances unequivocal evidence of Hodgkin's granuloma is present.

Generalized weakness is not infrequently the first symptom, and in the absence of obvious lymphadenopathy or splenomegaly may be a most difficult one to evaluate. A careful search should be made for enlarged lymph nodes and abdominal masses, and the finding of an elevated basal metabolic rate or an elevated white-cell count with an increased percentage of polymorphonuclear neutrophils may be of some diagnostic significance.

Not infrequently, symptoms referable to the gastrointestinal tract first attract the patient's attention. If there has been melena or hematemesis, some intrinsic lesion is usually discovered at autopsy. Other symptoms, such as anorexia and nausea, can only rarely be traced to such an intrinsic lesion.

Finally, there are a considerable number of the most varied initial signs and symptoms, such as anorexia, edema of the legs, dyspnea, loss of weight, abdominal masses, cough, generalized itching, amenorrhea, hemoptysis, persistent sore throat, vomiting, hematemesis, dysphagia, melena and deafness. One can only bear in mind that Hodgkin's granuloma may first manifest itself in such ways and endeavor to prove whether it is present.

In a considerable number of cases there is initially a combination of several symptoms, in which event the condition is usually already well advanced. Yet it should be pointed out that this fact by no means necessarily militates against relatively successful therapy.

It is thus clear that Hodgkin's granuloma is usually first manifest by painless cervical lymphadenopathy, but that its initial stage may be marked by the most diverse symptoms and signs.

General Course

In the great majority of cases, Hodgkin's granuloma progresses inexorably to a fatal termination, but the course is extremely variable, and aside from the broadest generalities, it is impossible in any given case to predict what changes will take place or precisely when they will occur. Virtually any organ or tissue in the body may be involved, and the clinical course of the disease depends in large measure on the extent and rapidity of the spread as well as on which organs are involved. In one case, the pathologic changes may become so widespread and so all-inclusive that no organ can properly fulfill its function, and death ensues from a sort of general attrition; in another, sudden death may occur at a time when the patient seems to be in comparatively good health.

The disease does not advance in an even, orderly fashion. Remissions occasionally occur in a quite unpredictable manner, and patients who have seemed to be failing under the best of treatment may unaccountably respond most favorably to what is regarded as a final threapeutic gesture. On the other hand, it is not unusual to see a patient who has been doing especially well for many months or even years become rapidly worse and die within a few weeks.

In view of these facts, it seems profitless to attempt any working classification of the various clinical types that are met with in practice. It is true that in one case, the process may be confined largely to the mediastinum, in another to the spleen and in still another to the gastrointestinal tract. In some cases anemia is a marked feature, in others high fever. A patient may be seen in whom loss of weight and strength has been, from the onset, a striking feature; again, a patient may be able to continue hard physical labor until the end is but a short way off. In this sense, there are clinical types, yet each case is a law unto itself, and the disease can be treated more intelligently if this fact is constantly borne in mind.

Hodgkin's granuloma only rarely progresses sharply into Hodgkin's sarcoma, a far more malignant form of the disease. Such transformation is far less frequent than the comparable progression of Hodgkin's paragranuloma into Hodgkin's granuloma.

The following cases illustrate the varied course of Hodgkin's granuloma.

Case 8. C. C. (C. H. 167400), a 6-year-old girl, was admitted to the hospital on January 1, 1933. The past history was irrelevant. She had always seemed healthy. Approximately 3 weeks before entry, the parents had noticed enlarged lymph nodes in each side of her neck. These increased rapidly in size, and a week later she developed a severe cough, associated with some hoarseness and a moderate elevation of temperature. For a week before entry, she had had marked anorexia.

Physical examination on admission revealed a well-developed and well-nourished girl suffering from a marked degree of dyspnea. In the anterior posterior triangle of both sides of the neck were numerous rubbery lymph nodes 1 to 4 cm. in diameter. They were not attached to the skin or to the underlying tissues. The throat appeared normal. Examination otherwise revealed nothing abnormal except for a pronounced widening of the mediastinal dullness, a finding that was confirmed by x-ray examination. The temperature was 102°F., the pulse 140, and the respirations 30. The red-cell count was 3,800,000 and the white-cell count 13,400, with 72 per cent polymorphonuclear neutrophils, 2 per cent myelocytes, 20 per cent lymphocytes and 6 per cent monocytes. A biopsy of one of the cervical lymph nodes showed the picture of Hodgkin's granuloma. The patient's dyspnea increased, the temperature rose to 104°F., and she died of respiratory failure less than a month from the apparent onset of her condition.

Case 9. K. A. D. (H.H.36-542), a 20-year-old man, was admitted to the hospital on May 25, 1936. A year before entry, he had had a mild upper respiratory infection, following which there had appeared an enlarged lymph node in the right side of the neck. There was no impairment of general health. The node was neither tender nor painful, but it persisted after the subsidence of the respiratory infection. Eight months later, the patient's family noticed that he was becoming pale. For several weeks before admission, he ran a septic type of temperature and had many drenching night sweats. Shortly thereafter, there appeared edema of the ankles and scrotum, and coincidentally both the hearing and vision began to fail.

Physical examination on entry showed an emaciated man lying apathetically in bed. His vision was markedly impaired, and he could not read the largest newspaper type. The left eye showed a moderate degree of enophthalmos and was deviated downward and inward. The right fundus oculi showed several patches of exudate similar to that seen in chronic nephritis, and in addition a large area of chorioretinitis on the temporal side of the disk. In neither ear could the patient hear the tick of a watch. Both nostrils were filled with clotted blood, and the lips were parched, cracked and bleeding. In the right side of the neck from the angle of the jaw to the supraclavicular space were many firm, discrete lymph nodes averaging 2 cm. in diameter. Recently there had been excised from this region a lymph node showing the typical picture of Hodgkin's granuloma. In each groin were large numbers of firm, tender lymph nodes, and many similar ones could be felt deep in the pelvis above the pelvic brim. The heart was normal in size. Signs of moderate ascites were present, but neither the liver nor the spleen could be felt. There was marked edema of both legs and of the scrotum and penis. The red-cell count was 2,130,000, the hemoglobin 30 per cent (Sahli), and the white-cell count 2000, with a normal differential count. The platelets were greatly diminished. The urine contained a slight trace of albumin and a few red cells. The temperature was 103°F., and the pulse 130.

Since the disease was obviously widespread, involving the central nervous system, ears, eyes, chest, abdomen, pelvis, bone marrow and peripheral lymph nodes and since his condition seemed desperate, it was decided to give several blood transfusions before instituting x-ray therapy. In addition, he was put on a high-caloric diet.

Between May 26 and June 11, three blood transfusions totaling 1600 cc. were given, with the result that the hemoglobin rose to 50 per cent and the red-cell count to 3,500,000. During the interval, his general condition remained essentially unaltered but, interestingly enough, the hearing improved sufficiently so that the patient could hear a watch tick in both ears and could understand normal conversation. The eyesight also improved, although not to the same extent. The patient's condition appeared to warrant the institution of x-ray therapy, and inasmuch as the most marked lymph-node involvement was in the pelvis, radiation was directed to that area, and from June 11 to 15 he received 275 r of high-voltage x-rays. He suffered no untoward reaction to this small amount of radiation, so that between June 15 and 22 he was given 1000 r to the abdomen. The temperature remained elevated, the physical examination was essentially unaltered, and the general condition seemed, if anything, rather worse. The patient became jaundiced and even during the day was somewhat drowsy. He took no notice of his surroundings, and it was difficult to arouse him from his almost constant lethargy. The red-cell count had fallen to 1,940,000 and the hemoglobin to 32 per cent.

The outlook was certainly not bright, and all therapeutic measures to date appeared to have been unavailing. In view

of the falling red-cell count, the patient, between July 1 and 10, was given transfusions totaling 3000 cc. of blood, with a resultant rise of the red-cell count to 3,480,000. By that time, the temperature had come down to normal, the hearing was normal, and the eyesight, although still poor, was much improved. The patient was allowed up and around the wards within the limits of his strength. His appetite, which on admission had been practically nil, was now ravenous. His general condition improved daily, and he rapidly gained both strength and weight. The emaciated, apathetic boy first seen became an optimistic young man. The lymph nodes in all areas became much smaller. The ocular manifestations improved, with the exception of the retinal changes, which remained unaltered. The peripheral edema and ascites disappeared. On July 20, the patient was given another blood transfusion of 500 cc., and on July 25 he walked out of the hospital to return to his home.

In August of the same year, the cervical lymph nodes returned and increased rapidly in size, but after administration of 600 r to each side of the neck they completely disappeared, and the patient seemed in excellent condition and was able once more to return to work as a laborer.

He continued to work at hard manual labor until December, 1936, when he again became weak and complained of anorexia, nausea and vomiting and ringing in the ears. There were many firm lymph nodes in each side of the neck. The mediastinal shadow was increased to the right, and the spleen was palpable 3 cm. below the costal margin. The temperature was 103°F., the pulse 130, and the respirations 35. Examination of the blood showed a red-cell count of 1,570,000 and a white-cell count of 4000. The patient was given three blood transfusions of 500 cc. each and 75 r of spray x-ray therapy, both anteriorly and posteriorly. Following this, his general condition improved greatly, the lymph nodes and spleen disappeared, and he was once more able to resume his normal activities. In May, 1937, however, he was again troubled with anorexia and vomiting, and the temperature rose to 102°F. The spleen was barely palpable on inspiration. Many fine rales appeared at the apex of the right lung. There was no return of the lymph-node enlargement, but the patient failed steadily, and again became partially blind and deaf. The temperature remained constantly between 101 and 103°F., the red-cell count fell to 2,630,000, and the patient died on August 25, 1937, which was 2 years and 3 months after the date of his first symptom.

Case 10. E. M. (P. H. 1887), a 52-year-old man, was in excellent health until May, 1929, when he noticed a small lump in the left axilla. It was neither painful nor tender, and he had no other complaints. Physical examination showed a firm mass 6 cm. in diameter high in the left axilla, a pea-sized lymph node above the left clavicle and a similar one in the left epitrochlear region. Otherwise, the examination showed no abnormalities. The red-cell and white-cell counts were within normal limits, and x-ray films of the chest failed to show any widening of the mediastinal shadow. The axillary and epitrochlear nodes were excised, and each showed the typical histologic picture of Hodgkin's granuloma. The patient was given 900 r to the left axilla and 600 r to the left epitrochlear region.

There have been no recurrences, and the patient has remained well to date, 15 years from his first symptom.

Case 11. J. P. (P. H. 2757), a 48-year-old, Italian laborer, noted in August, 1930, ease of fatigue, anorexia, night sweats and a mass in the left axilla; he continued at his work, however. Three months later there appeared an enlarged lymph node in the right axilla. This was removed and showed the usual picture of Hodgkin's granuloma. He was admitted to the hospital on December 6, 1930.

Physical examination revealed a firm, nontender lymph node 4 cm. in diameter in the left axilla and several similar ones in the left supraclavicular area. The spleen was palpable 3 cm. below the costal margin. An x-ray film of the chest was normal, and it was specifically noted that there was no evidence of bone involvement. The general condition was good. The red-cell count was 3,850,000, the hemoglobin 60 per cent (Sahli), and the white-cell count 11,400, with 79 per cent polymorphonuclear neutrophils, 1 per cent eosinophils, 15 per cent lymphocytes and 5 per cent monocytes. Six hundred r was given to the left side of the neck, with rapid disappearance of the nodes. Three weeks later, however, the patient noticed a raised, tender swelling 6 cm. in diameter over the lower part of the sternum. X-ray films showed an extensive irregular mottling and destruction of the gladiolus, and on physical examination there was a hard, tender swelling rising 2 cm. above the general level of the sternum and 10 cm. in diameter. The patient was given 600 r to the left side of the neck, each axilla and the spleen and 1000 r over the sternal mass. The nodes disappeared following this treatment. The sternal mass became much smaller, but did not disappear.

During the intervening years, he has received 2400 r to the involved area. The last x-ray films still showed the bony destruction, but when last seen in the spring of 1944, 15 years after his first symptoms, the patient was feeling perfectly well and was capable of doing reasonably hard manual labor.

Cases 10 and 11 attest the value of early treatment, and show that Hodgkin's granuloma is not always so rapidly fatal as is generally believed.

Case 12. A.P. (H. H. 17–646), a 10-year-old boy, in 1915 noticed a plum-sized mass in the right side of the neck. This was excised and showed the histologic features of Hodgkin's granuloma. Physical examination revealed no other abnormalities, and both the past and family histories were noncontributory. The peripheral blood picture was normal. At intervals during the next 8 months, 8200 m. c. h. of radium was given at the site of the lesion and 800 m. c. h. to the mediastinum.

For the next 15 years, the patient remained entirely well, except that from time to time minute nodes were noted under the anterior part of the jaw. This minor lymphadenopathy appeared to be due to oral sepsis.

In 1930, at a routine checkup, there was found a mass the size of a small plum in the submaxillary region on the left side. This was removed and again showed the picture of Hodgkin's granuloma. An indeterminate amount of x-ray (probably about 600 r) was directed at the left side of the neck. The patient thereafter remained free of all signs and symptoms up to December, 1941, when he moved to another city and was lost sight of.

Whether this result can properly be regarded as a cure in the true sense of the word is perhaps debatable. That the results were excellent no one can deny, for the patient was alive and well nearly 30 years after the initial lymphadenopathy.

Hodgkin's Sarcoma

Pain is the most frequent initial symptom of Hodgkin's sarcoma (Table 3). It is most frequent in the abdomen, is usually unrelated to meals,

Table 3. *Initial Symptoms of Hodgkin's Sarcoma (32 cases).*

Symptoms		No. of Cases
Pain		17
Abdomen	9	
Lymph nodes	4	
Chest	2	
Throat	2	
Painless enlargement of lymph nodes		8
Weakness		5
Loss of weight		5
Dyspnea		4
Cough		3
Vomiting		3
Sore throat		2
Anorexia		2

and is occasionally accompanied, even early in the disease, by loss of weight. Pain may, of course, occur elsewhere, and it is to be particularly noted that the superficial lymph nodes are often painful. This is rarely the case in Hodgkin's granuloma. Painless lymphadenopathy may be the sole initial

symptom, but the enlarged lymph nodes seldom fluctuate in size as they frequently do in Hodgkin's granuloma. Weakness, dyspnea, cough and vomiting may be seen early. Rapid loss of weight is much more frequent than in Hodgkin's granuloma and may be the outstanding feature of the disease. Thus, pain was an initial complaint in over 50 per cent of our cases of Hodgkin's sarcoma, whereas it was present initially in only 12 per cent of patients suffering from Hodgkin's granuloma. Symptoms suggesting involvement of internal organs were noted at onset in 75 per cent, whereas they were present in less than 30 per cent of the patients suffering from Hodgkin's granuloma.

On the average, patients sought medical advice within five months of the apparent onset of their disease, yet even after this short interval the initial complaints had been almost invariably supplemented by many others, and during the course of the disease, still further symptoms reflect the rapidly invasive and malignant character of the tumor.

TABLE 4. *Symptoms During Course of Hodgkin's Sarcoma (32 cases).*

SYMPTOMS	NO. OF CASES
Fatigue	28
Loss of weight	26
Pain	21
Dyspnea	16
Anorexia	14
Cough	14
Edema	13
Fever	8
Constipation	7
Vomiting	7
Epistaxis	4
Hematuria	3
Jaundice	3
Night sweats	3
Chills	3

The disease runs an insidiously rapid course even though the initial response to x-ray therapy may have appeared to be good. Fatigue and rapid loss of weight are frequent. The majority of patients develop pain referable to the organs or tissues involved, and often there is cough due to the frequent involvement of the lung. Fever, on the other hand, is rare; by contrast its frequency in Hodgkin's granuloma is well known. Symptoms and signs referable to the various organs will be discussed in more detail in a subsequent paper. In general, it may be said that Hodgkin's sarcoma runs the course of a highly malignant neoplasm.

The following cases illustrate the course of the disease.

CASE 13. G. P. (B. C. H. 92408), a 37-year-old man, entered the hospital in October, 1929, because he had had epigastric distress for the previous 2 months. The pain was constant, radiated to the umbilicus and was greatly aggravated by the ingestion of food. There had been no vomiting, hematemesis, melena or jaundice. There were no other symptoms of importance, and the past history was irrelevant.

On physical examination, a freely movable mass the size of an orange was felt in the epigastrium. In each axilla and in each side of the neck were several firm lymph nodes 4 to 5 cm. in diameter. The spleen was felt 3 cm. below the costal margin. There were no other abnormalities of note. The temperature was normal. The red-cell count was 4,000,000, the hemoglobin 92 per cent (Sahli), and the white-cell count 25,000, with 75 per cent polymorphonuclear neutrophils, 23 per cent lymphocytes and 2 per cent monocytes. Biopsy of one of the axillary lymph nodes showed Hodgkin's sarcoma.

Six hundred roentgens of x-ray therapy was given to the abdomen and to the nodes in the axilla and neck. Two weeks later, neither the epigastric mass nor the superficial lymph nodes could be felt. The response to radiation was dramatically satisfactory, and for 6 months the patient felt perfectly well. In April, 1930, however, he returned to the clinic and enlarged lymph nodes were found in the cervical, axillary, inguinal and popliteal regions. No abdominal mass could be felt. Six hundred roentgens of x-ray therapy were given to each involved area, but there was little if any subsequent improvement in the patient's condition, in spite of this dosage and subsequent additional x-ray therapy. Indeed, he soon began to complain once more of severe epigastric pain, especially after meals, and of vomiting, weakness and marked loss of weight.

In August, 1930, the patient was readmitted. At that time, there were in each side of the neck and in each axilla firm lymph nodes 10 cm. in diameter that were neither fixed nor tender. The spleen was found to be 5 cm. below the costal margin, and the liver was barely palpable on deep inspiration. The red-cell count had fallen to 1,230,000 and the hemoglobin to 35 per cent (Sahli). The white-cell count was 2550, with 90 per cent polymorphonuclear neutrophils, 8 per cent monocytes and 1 per cent lymphocytes. The urine examination was negative.

From then until his death 3 weeks later, the patient ran an irregular fever to 100°F. and the pulse gradually rose from 90 to 130. The right leg became edematous, presumably from pressure of lymph nodes in the inguinal region, and in the right parietal bone of the skull there developed a palpable defect. X-ray examination showed a large erosion of the skull in this region. Many petechiae appeared in the skin of the chest and abdomen and in the mucous membranes of the mouth. The patient failed steadily and died on August 20, 1930, just a year after the appearance of his first symptom.

Autopsy showed Hodgkin's sarcoma involving the retroperitoneal, mesenteric, mediastinal, cervical, axillary and inguinal lymph nodes, as well as the spleen, liver, kidneys, pancreas, adrenal glands, duodenum, ileum, colon, lumbar vertebras and skull.

CASE 14. P. C. (H. H. 24-806), a 49-year-old man, was first seen in June, 1924, at which time he complained of pain in the throat. Two and a half months before entry, he had had frequent sore throats. Otherwise, the history was noncontributory.

On examination, the right tonsillar fossa was found to be occupied by an ulcerated tumor 6 cm. in diameter. It was not bleeding. A moderately large, firm lymph node was palpable beneath the angle of the right mandible. No other abnormalities were noted on physical examination. The patient was instructed to return 1 week later for biopsy and further study, but he did not reappear until September, 3 months afterward. In the interim, his sore throat had recurred at irregular intervals without any specific treatment. Examination showed in the right tonsillar region a tumor that extended high up into the nasopharynx. No lymph nodes were felt in the neck. There were no other abnormalities. The red-cell count was 5,800,000, the hemoglobin 95 per cent (Sahli), and the white-cell count 5600 with 55 per cent polymorphonuclear neutrophils, 37 per cent lymphocytes, 5 per cent eosinophils and 3 per cent monocytes. A biopsy was performed, and the lymph node removed showed all the characteristics of what we now call Hodgkin's sarcoma.

In November, 1924, eight radium seeds of 1 m.c. each were implanted in the tumor, and within 6 weeks it had completely disappeared. The patient remained asymptomatic for 6 months.

In June, 1925, he again developed a sore throat, and the left tonsil was found to be enlarged and ulcerated. Implantation of radium seeds (four of 1.5 m.c. each and two of 1 m.c. each) resulted in rapid shrinkage in the size of the tumor. In September of the same year, a mass of lymph nodes was palpable in the left side of the neck. One so-called "suberythema dose" of high-voltage x-ray was given over this area. For the next 16 months, the patient felt perfectly well and did not report to the follow-up clinic.

In February, 1927, he returned complaining of recent difficulty in breathing, severe headache and a painful mass in the neck. The pharynx appeared normal, but there was a bloody discharge from the almost completely obstructed nasal passage and a hard, walnut-sized lymph node was found in the right side of the neck. An x-ray film of the chest disclosed enlarged mediastinal lymph nodes. High-voltage x-ray therapy was given to the thorax and neck, without any beneficial effect. The development of deafness, diplopia, right unilateral exophthalmos and finally blindness bore witness to the rapid extension of the neoplasm within the skull. The patient died on April 22, 1927, just 3 years after the first symptom.

Autopsy showed a tumor having the histologic features of the condition now referred to as Hodgkin's sarcoma, which was primary in the right tonsil. There was direct extension to the nasopharynx, sphenoidal sinus, right orbit, right temporal bone, pituitary gland and dura mater. Metastases were found in the pancreas and mesenteric lymph nodes.

CASE 15. J. C. (B. C. H. 974896), a 53-year-old woman, was admitted to the hospital on February 14, 1940, with the chief complaint of "gas on the stomach." The past history was entirely noncontributory. For 3 weeks prior to admission, she had noted that during or immediately after meals she felt "bloated," and there had been almost constant nausea. Anorexia had been extreme, and she had grown progressively weaker.

Physical examination revealed several enlarged, rubbery lymph nodes behind the left sternomastoid muscle. Otherwise, there were no notable abnormalities. Gastric analysis showed absence of free hydrochloric acid, and both the gastric contents and the stools gave a strongly positive guaiac reaction. The red-cell count was 5,100,000, the hemoglobin 71 per cent (Sahli) and the hematocrit 37. The white-cell count was 4600, with 68 per cent polymorphonuclear neutrophils, 10 per cent lymphocytes, 17 per cent monocytes, 4 per cent eosinophils and 1 per cent basophils. The temperature, pulse and respirations were normal.

A gastrointestinal series showed no abnormality in the esophagus, but x-ray examination of the stomach revealed a large fungating tumor arising near the cardia. The mass appeared to encroach on the esophagus but caused no obstruction. The remainder of the gastrointestinal tract appeared normal.

The patient became increasingly short of breath and failed rapidly. The lymph nodes in the neck increased greatly in size, and within a week there developed signs of obstruction of the superior vena cava. Fluid accumulated in the left pleural cavity, and 2 months after admission 900 cc. of bloody fluid was removed. Anorexia became extreme, and the patient died on April 19, a scant 3 months after the first symptoms.

Autopsy showed extensive involvement of the greater curvature of the stomach by Hodgkin's sarcoma, with direct invasion of the pancreas and diaphragm, massive serous effusion in the left pleural cavity and extensive involvement of the abdominal lymph nodes.

* * *

From the case histories and the discussion above, it should be clear that in broad terms Hodgkin's paragranuloma is a comparatively benign condition occasionally progressing to Hodgkin's granuloma; that Hodgkin's granuloma is characterized by the most protean manifestations, is usually, though by no means invariably, fatal within a few years, and on rare occasions progresses to Hodgkin's sarcoma; and finally that Hodgkin's sarcoma behaves as a highly malignant, comparatively localized tumor rapidly resulting in death.

VENEREAL DISEASE AS A WAR INJURY*

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VICTORY in the shortest possible time is our objective. It is the duty of every one of us to do all in his power to prevent delay. Morbidity in the armed forces, or among the men and women who produce the munitions without which the fighting men cannot hope to achieve victory, is something that concerns us as physicians. Every case of morbidity among these people is a war injury, and among such cases venereal diseases are high on the list.

During all previous wars in which this country has engaged, the incidence of gonorrhea, and to a lesser extent that of syphilis, has been appalling. The cause of high venereal-disease rates during wartime is largely psychologic. When large numbers of people become affected by war hysteria, a marked increase in sexual promiscuity results. Since promiscuity is the cause of the wide dissemination of the venereal diseases, the less there is in a given group the lower will be the venereal-disease rate. If it were possible to have everyone adhere to the one-man, one-woman ideal, venereal disease would disappear in one generation. Although there appears to be no hope of attaining such an ideal in the near future, it is a goal toward which society should constantly strive.

Before Pearl Harbor it was my privilege to talk with many high-ranking line officers, most of whom had a sound understanding of sex and venereal disease. An occasional officer, however, expressed himself paradoxically to the effect that a man could not be a good soldier unless he occasionally had sexual relations, but that any soldier so stupid as to acquire a venereal disease was not wanted in his command. As physicians we should like to know what diagnostic procedures the soldier was expected to utilize in order to eliminate the possibility of venereal disease.

Fortunately, the Army and Navy are officially committed to the repression of prostitution. Continence is their number-one approach to the venereal-disease problem. It is the duty of commanding officers to see that all men in their commands are given data about sex and venereal disease, particularly the fact that continence is compatible with manhood and good health. The armed forces are, however, realistic in that they concede that by the time a man is old enough to be inducted into the

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Army or Navy his sex habits have been quite well established, and that regardless of all efforts made in the field of sex education many of these young men will be sexually promiscuous. For such, venereal prophylaxis is advocated. There are those who on moral grounds argue against venereal prophylaxis. Their stand is due in part to the fact that some prophylactics are also contraceptives. There are prospects that a single, simple, clean, nonirritating prophylactic that is not contraceptive but is efficient against both syphilis and gonorrhea will soon be available. If so, it is hoped that much of the present opposition will disappear.

During World War I, the attempt was made to control venereal disease by punitive measures. Men were punished for failing to take a prophylactic after an exposure and also for acquiring a venereal disease. Consequently, a soldier's only chance of escaping punishment if he became infected with gonorrhea or syphilis was to conceal his illness. This was frequently done with more or less success by his going to some nonreputable agency for treatment. Often this resulted in his avoiding punishment, but it was notoriously ineffective from the standpoint of curing the infection and protecting public health. Punitive measures have failed in every venereal-disease-control program in which they have been utilized. The modern public-health attitude is to look on gonorrhea and syphilis as communicable diseases and not as crimes, and to consider a venereal infection as a public-health menace until it is brought under control. The most efficient way to get such infections under control is to offer the best possible diagnostic and therapeutic services without the necessity of the patient's losing all his or her self-respect, and to eliminate all punitive measures. The Army has adopted this intelligent attitude. A soldier who now acquires a venereal disease is punished only if he conceals it. He does lose pay for time spent in a hospital for a venereal infection but by authorizing the treatment of gonorrhea on a duty status the Army has made it possible for a man so treated to avoid forfeiture of pay. This is unquestionably good medical and sound public-health practice.

At the beginning of the present emergency, divisions of venereal-disease control were established in the offices of the surgeons general of the Army and Navy. It had long been recognized that if no one is specifically charged with the duty of controlling venereal disease there will be no control, but when certain persons are designated for such a specific duty much progress is made. This has been noted in many of the state health departments, in which during the last several years divisions of venereal-disease control have been established. Both services are to be congratulated for taking such an important step in connection with one of their major problems, and also for their wise selection of officers to head these branches. These well-trained, highly efficient officers are responsible for their respective control programs, which are based on the best scientific experience so far as it is compatible with the difficulties of military administration. It is obvious that in a theater of operation a venereal-disease-control program must be a compromise between what is the best and what is practicable. It is an old American custom for armchair strategists to point out errors of commission or omission in the conduct of wars. An impartial observer familiar with all the facts could find little if anything to criticize in the way the venereal-disease program is being run in the armed forces, both at home and abroad.

A large group of medical officers who have been given intensive courses of instruction in venereal-disease control are now stationed in the several service commands, naval districts and large military units, where they are functioning as venereal-disease (V.D.) control officers. That the venereal-disease sections are doing an excellent job is revealed by the present situation as contrasted with the past. Turner and Brumfield[1] state that during the last century rates of over 150 per 1000 per annum were not unusual in the Army. The annual rate for 1939 was 29.6 per 1000 per annum, which was the lowest recorded until that time. There are indications that the present rate is even lower. In 1940 the days lost as the result of venereal disease were 1278 per 1000 men, and in 1943 this figure dropped to 400. Although these figures indicate a decided improvement, there were nevertheless 2,824,000 hospital-bed days from January, 1942, to September, 1943, due to venereal disease, which means that there is still too much morbidity.

Every serviceman known to have gonorrhea or syphilis is interviewed by a medical officer who attempts to get from him the identity of his recent sex contacts. The information obtained is sent to the state department of health, whereupon trained epidemiologists attempt to locate the woman and to persuade her to go to some medical agency for an examination. This may be a private physician or a clinic. It is discouraging to note that, of the women who go to a private physician for diagnosis in Massachusetts, infection is detected in 53.2 per cent, whereas 71.6 per cent of those examined in clinics are found to be infected. These figures are statistically significant. It is known that many of the women who go to a private physician and are said to be noninfectious have been and continue to be identified by enlisted men as their only recent sex contacts. This suggests that some physicians are not willing to utilize the most efficient diagnostic procedures available. Some physicians have admitted that laboratory studies were not done because the woman did not have clinical evidence of infection. Experience during recent years indicates that many women found to be infected with gonorrhea do not show any of the so-called "typical" signs or symptoms of the disease.

Cultures, although far from perfect, are more efficient than any other known method in detecting

gonococci in women. No woman who admits a sexual contact and who has been identified as a possible source of a known infection should be diagnosed as not infected, no matter how normal she may appear on inspection, without at least one negative culture. The Massachusetts Department of Public Health will shortly announce a new regulation to the effect that whenever a woman is alleged to have been exposed to, or to have been, the source of a gonococcal infection the department shall require that there be one or more negative cultures of material taken from the urethra and cervical canal before it will accept a report that the person is free from infection. As a matter of fact, it would be a wise public-health measure to give a five-day course of sulfathiazole to all women who admit a recent exposure to a known case of gonococcal infection, regardless of negative laboratory findings. If this were done, many infections now overlooked would be cured, and this would probably lower the rate of infection in the services.

There have been no advances in therapy that are more electrifying than the newer methods of treating gonorrhea and syphilis. With the introduction of the sulfonamides from two thirds to three fourths of gonococcal infections were cured within two to five days, whereas previously cure had taken from two to five months. Today more than 95 per cent of all gonococcal infections, sulfonamide-resistant and sulfonamide-susceptible, can be cured with penicillin in eight to ten hours.

Frequently there is a considerable lag between the announcement of a new discovery by laboratory and clinical investigators and its adoption by the medical profession. There has been no hesitancy by the armed forces in adopting newer treatment methods for venereal disease. Existing methods have been altered immediately as soon as clinical trial has demonstrated something more efficient. For this the services are to be commended. Inasmuch as the armed forces are said to have an adequate supply of penicillin, it may be that in the near future all gonococcal infections in the services will be treated with this highly efficient agent.

Until a few months ago servicemen with gonococcal infections were given a course of chemotherapy, and if this did not result in cure they were given a second course after an interval of two or three days. Those who were not cured by the second course were, so far as facilities permitted, sent to a general hospital for fever therapy. Fever therapy has now been discarded in favor of penicillin, and it was recently announced that military personnel with gonococcal infections would be given but one course of sulfathiazole, and that if this failed to cure they would be given penicillin without further delay. It may appear fantastic, but it is nevertheless conceivable that the Army could provide facilities in infirmaries where men with gonococcal infections could report at six o'clock in the afternoon, go to bed and be given an injection of penicillin every two to three hours during the night, and be discharged to duty at 6 or 7 o'clock the next morning, cured of their infections. This would mean that the loss of man power due to gonorrhea would be almost negligible.

Between March 13 and April 30 of this year, 77 patients with sulfonamide-resistant gonococcal infections—60 men and 17 women—were treated with penicillin in the Out-Patient Department of the Massachusetts Memorial Hospitals. Each received a total dosage of 90,000 Oxford units given in divided doses from 9 a.m. to 5 p.m. on the first day and one injection on the morning of the second day. Positive cultures were obtained from every case just previous to the beginning of treatment. Cultures were done at two-hour intervals during the first day and daily thereafter for three days, and then once a week for three weeks. In only 2 cases were positive cultures obtained after the first injection. In one the culture was positive two hours after beginning treatment but all subsequent cultures were negative. In the second case a positive culture was obtained twenty-four hours after beginning treatment but all cultures on succeeding days were negative. Further experiments are being conducted for the purpose of working out a system of therapy whereby it will not be necessary for patients to give up an entire day to the treatment.

With such an efficient therapeutic agent as penicillin, one is justified in looking forward to the day when gonorrhea will be an extremely rare disease. There is much to be done, however, before that time will arrive. A male patient, who reported to us from another clinic and who had had his infection for thirty days, responded immediately to treatment clinically and bacteriologically. Subsequently, following a sex contact with his wife, he became reinfected. Cultures done on his wife were positive, whereupon she was treated with penicillin and the husband was re-treated, with the result that they are both now negative. It will be necessary to get all women now infected under treatment before the job can be completed, and this is something that will take time and perseverance.

There is a trend in military and civilian hospitals to have gonorrhea treated in medical rather than urologic or gynecologic departments. Turner and Sternberg[2] report as follows:

> It can be said categorically, it is in those Army hospitals in which reliance is placed on internal medication and forced fluids to the exclusion of local treatment that the best results are being obtained. Nothing appears to be gained by urethral instillations, prostatic massage or the passing of sounds in the ordinary case of uncomplicated gonorrhea, and the proportion of complications appears to be significantly higher where these procedures are employed.

The Army's experience is similar to that of many clinicians: therefore, the medical department seems to be the logical place for treating gonorrhea.

No one yet knows whether penicillin is capable of curing syphilis. Certain facts are known, and these are most encouraging. Mahoney's[3] first 4 cases, which were given an eight-day course of treatment, have been observed for eleven months. All became dark-field negative within a few hours after the first injection. This was followed by an early healing of the lesions and a steady drop in the syphilitic reagin titer, and all the serologic tests became negative. None of these patients has yet had a clinical or a serologic relapse. The spinal fluid in each case is negative. Whether or not they have been cured of syphilis will not be known until they have been observed for a considerable period. Since Mahoney's original work many other patients with early syphilis have been treated with penicillin, and although the observation periods have not been sufficiently long to justify final conclusions, their progress to date more or less parallels Mahoney's results.

The modern trend in the arsenotherapy of syphilis is to concentrate the curative dose in the shortest possible time. The highly publicized five-day treatment stimulated some much needed investigations. The old standard eighteen-month continuous alternating system, although efficient and relatively safe, was unsatisfactory in that throughout the country probably not more than 15 per cent of those with early syphilis received what was considered to be adequate treatment. Shortening the time of treatment may be expected to increase this figure.

Many modifications of the five-day treatment have been advocated; one-day drug and fever, five-day intravenous drip, ten-day multiple injection, and thirty-day, eight-week, ten-week and twelve-week schedules, all designed to give a curative dose of Mapharsen. It is known that a given amount of Mapharsen has a definite therapeutic index, whether given in five days or several weeks, but that the shorter the time the greater is the risk of toxicity.

All systems of arsenotherapy cause a certain amount of morbidity, most of which is mild but nevertheless undesirable. No cases of morbidity as the result of penicillin therapy have been reported. This fact seems to be of great importance to the armed forces. If it should be established that penicillin is as efficient as the arsenicals, a great advance in medicine will have been made.

* * *

Although gonorrhea and syphilis are still important causes of morbidity in the armed forces, they are relatively less so than in any previous mobilization. This is due first to the fact that the Army and Navy both have capable organizations whose specific job it is to control venereal disease, and second to the immediate utilization by the services of the almost unbelievable advances that are being made in the therapy of these diseases.

Morbidity from venereal disease can be further reduced. This would mean fewer noneffectives in the armed services and on the home front. It is unquestionably our duty to bring this about at this critical time when it is imperative that we do our utmost to eliminate everything that may impede victory.

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SURGICAL EXPERIENCES WITH THE WOUNDED OF THE BUNA CAMPAIGN*

Colonel Augustus Thorndike, M.C., A.U.S.

MAJOR General Norman T. Kirk, the Surgeon General of the Army, has stated that out of every 100 wounded in battle in this war 97 may be expected to survive. This is truly a glowing tribute to modern military medicine. All those who have husbands, sons or brothers in combat may take heart and gain great hope that their nearest of kin, if wounded, have a very good chance of returning home. It is my duty to report any thoughts and any facts that we with overseas experience in military service can pass on, even though they concern a minor fraction of the total experience in caring for the sick and wounded of the Army.

The title confines my remarks to an action with the enemy — the first participated in by our Army ground forces that occupied a period of approximately twelve weeks from early November, 1942 — the Buna Campaign in New Guinea. On reaching the continental United States it seemed strange that little general interest had been gained concerning the Southwest Pacific theater. To be sure, the action to be described was not one participated in by large bodies of troops, but it was an important engagement, and particularly so in respect to the soldiers who were taking part in it. Those decorated with the Purple Heart will never forget that experience — they carry scars that have a meaning. The nearest of kin of those killed will remember this engagement. Good surgery near the line of combat saved many lives. Native litter bearers performed heroic service in evacuating the sick and wounded on hand-hewn litters. Up to this date the Fifth Air Force has evacuated more than

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85,000 patients — a larger number than in any other theater.

Perhaps the most valuable development in military medicine in this theater concerning the care of the sick and wounded was the organization, development and operation of the portable surgical hospital. It is appropriate that credit be given to those particular units that pioneered in this early action. The general hospital, with which it was my privilege to serve, provided two such units, each commanded by a member of this society — Major Neil W. Swinton and Major George A. Marks. The portable hospital is a new development of this war, advisedly designated portable since the entire tentage, mess and surgical equipment and medical supply are carried on the backs of the personnel. Jungle warfare in a wet tropical atmosphere handicaps land transport to such an extent that the human pack is the only method of movement in the most advanced forward areas. Wards and operating rooms were tents, and beds were cots or litters elevated above the ground to avoid flooding. The personnel slept in "jungle beds." In the Buna Campaign selection of the site of the hospital was the really important requirement for reasonably comfortable operation of the hospital. Blackout requirements were enforced, and night operating was done with little or no ventilation. Because of the heat, the personnel were stripped to the waist.

Surgical care of the wounded was first carried out on the field of battle, where necessary dressings were applied; litters then bore the patient to the rear. Emergency care and necessary splinting were provided at the battalion aid station. From there, by litters or walking, depending on the location and type of the wound, the wounded were carried or directed to the portable surgical hospital, where major surgery or fracture reduction and splinting, where indicated, was accomplished. The patient was anesthetized, preferably with Sodium Pentothal but sometimes by spinal or local anesthesia. Blood plasma was used entirely as a substitute for whole blood, and saline and dextrose solutions for infusions. Fluid loss in perspiration was a constant factor in the tropics. The drugs used chiefly were the sulfonamides, quinine, tetanus toxoid and morphine. Nursing care was difficult in particular at night, when the only light was that from a hooded flashlight. Feeding patients hot food and caring for the usual sanitary requirements entailed by a bedpan were tedious and most trying tasks. The patients, however, received the best housing and the best medical and nursing care available within hundreds of miles, and remained in the hospital several days or until they could withstand the next stage of evacuation.

In reviewing the surgery later seen at the general hospital, one can but marvel at the results. One wonders why elaborate surroundings are required when such results can be obtained in the most primitive environs. It was proved, however, that good and better surroundings were necessary for wound healing and more efficient bed care for eventual recovery. In other words, for only a few days did the patient gain in his primitive jungle surroundings.

The surgical procedures carried out have been described by Major Marks in a graphic account of his portable surgical hospital, published in the December, 1943, issue of the *Bulletin of the United States Army Medical Department*. At present he is acting as assistant to the surgical consultant in that theater, and doubtless will have more to describe when he returns. In his present assignment, he is putting to practical use his invaluable experience of this early campaign. Major Swinton, now commanding a field hospital at the advance base, will likewise have much to tell.

In considering the types of wounds and the surgery carried on, one should be cognizant of the weapons used by the enemy. Machine guns, small arms, grenades and mortars were the principal weapons employed by the Japanese. What artillery there was, was put out of action early in the engagement. Sniping was the favorite mode of fighting. Therefore, one would expect penetrating bullet wounds to be the most frequently encountered. Wounds of the soft parts were most frequent, many involving the peripheral nerves, bones and joints and about 70 per cent involving the extremities. Less frequently the head, chest and abdomen were hit. The booby trap, if it existed, was not mentioned by those evacuated to our general hospital. Any record of surgery under the circumstances described above should be judged in two phases — the immediate result and the condition of the wounds and fractures when the patient arrived at the general hospital. In both categories it is a pleasure to report a mortality of 3.6 per cent, including all wounded cases at the portable surgical hospital. This proved that excellent surgery had been done. The general hospital patient arrived in excellent surgical condition after over 1000 miles of travel.

Every surgical procedure carried out with the most modern concept of conservative débridement and fracture reduction and with sound judgment, proved to have been correct. The usual procedure for the surgical treatment of wounds consisted in dusting sulfonamide powder into the débrided wound and providing a gauze drain, and encasing the extremity in plaster of Paris slabs. Alignment of fractures at the time of débridement and application of plaster were essential, and only a few of these patients lost position in transit, this being corrected at the next hospital stay. Head wounds did not do so well if above the level of the mandible. Chest wounds were usually penetrating and through-and-through, accompanied by rib fracture and hemothorax and occasionally by infection. Abdominal

wounds were infrequent, generally requiring closure of bowel perforations, rarely resection. There is no better criterion of the quality of the early surgery performed than to observe the later convalescence at the general hospital.

No complication of wound healing was more irksome than fungus diseases of the skin. Many forms of pathogenic fungi exist in this humid jungle and constantly attack the combat soldier. Figures on tetanus and gas infection are not available.

Five factors played an important role in the care of the sick and wounded of this campaign. All five co-ordinated well, resulting in the saving of many soldiers. Without good surgery at a forward area, without plasma, without chemotherapy, without native carriers and without air evacuation, this could not have been accomplished.

* * *

Possibly I should have described the surgical care of the wounded in this campaign. The care of the wounded soldier, however, involves more than the actual surgical care. The soldier, sailor or marine deserves the best. Perhaps it seems wise to illustrate the philosophy of the soldier by quoting excerpts from a letter written by a marine about to embark for overseas and found on his bed at the staging area after his departure: "Nurture strength of spirit to shield you in sudden misfortune . . . . Try not to distress yourself with dark imaginings; many fears are born of fatigue and loneliness . . . . And whether or not it is clear to you, no doubt the universe is unfolding as it should." That represents a creed, a faith, a trust and a purpose worth noting. Our soldiers are the best, and they look to the medical department of the Army or Navy for the best service. It is our obligation to determine that the medical service rendered is worthy of this marine's faith and trust. Speaking as one who has seen, it is a privilege to report that the wounded soldiers are receiving the best possible medical care.

MEDICAL PROGRESS

ANTIBIOTICS AND BACTERIOSTATICS IN BLOOD AND BODY FLUIDS

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IN the use of therapeutic agents of a chemical nature, it has become increasingly important to determine the concentration of the drug that circulates in the blood stream. For generations American chemotherapeutic agents have been thought of in terms of dosage, that is, the amount to be injected or ingested at a single administration. The modern concept more closely approaches the European meaning of the term "*dosage*," that is, the concentration of effective agent produced. It is becoming more and more essential to maintain the concentration of pharmacotherapeutic agents within certain limits.

If this is not done, two difficulties may ensue. If the concentration is too low, the drug will not be effective and fastness to the drug may ultimately develop. If, on the other hand, the concentration is too high, the danger of toxic symptoms and untoward side reactions becomes increasingly great. To steer through this Scylla and Charybdis must be the goal of the best therapy in the next decade.

In order to achieve this end, much more attention must be paid to methods whereby the approximate concentrations of circulating therapeutic agents can be determined easily and reliably. There are two general ways in which this can be done: first, the concentration may be determined directly in the circulating blood, preferably in the serum or plasma; second, in certain cases the urine may be viewed as a blood filtrate, when due regard must be paid to the time interval represented by a given sample. Usually the latter procedure is feasible only if the agent is stable and no considerable storage depots exist in the organism.

Although the present article is concerned primarily with antibiotics and bacteriostatics, it should be pointed out that this principle of dosage — in the Continental sense — probably applies to a considerable number of chemotherapeutic agents. It is known, for example, that in the relief of hypothyroidism the ultimate aim is to raise the concentration of circulating "hormonal" iodine to a level approximating 5 microgm. per 100 cc.[1] Similarly, there is evidence that in the use of digitalis glucosides it is not highly satisfactory to know only the amount administered daily.[2] The desired therapeutic effect will be approached much more closely if one considers the concentration of glucosides circulating in the blood stream.[3] Such facts raise the question whether dosage will ultimately be expressed in terms of milligrams or micrograms per 100 cc. of plasma rather than in amounts to be administered at a single moment.

This principle has become so evident in the case of the bacteriostatics and antibiotics, and the antibiotics are of such prime importance in the total war

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effort, that it seems desirable to summarize a few of the methods now available for clinical use. At present most of these are limited to large clinics, but there are indications that further simplifications will make them available even to the busy practicing physician so that he may carry on intelligent therapy. Indeed, it seems likely that many of the untoward effects that are reported through widespread use of the sulfonamides could be avoided if the amount of circulating drug were better known in the given case. To many local practitioners this may seem too much to expect, but probably the procedures involved will eventually be no more complicated than are many methods ordinarily used in clinical pathology.

Sulfonamide Compounds in the Blood, Body Fluids and Urine

The distribution of sulfonamide drugs in body fluids has been discussed recently in this journal by Davis,[4] who has discussed the possible mechanisms of their action.

The original method of Marshall[5] has proved to be so useful in the control of sulfonamide therapy that various modifications and improvements are important. One such advance has been suggested by Scudi and Jelinek.[6] This latest modification allows the color to be concentrated so that it is possible to measure highly diluted blood filtrates. Because the heterocyclic sulfonamides tend to be adsorbed by protein precipitates, it is especially desirable that protein be precipitated in dilute solution. The device suggested by Scudi and Jelinek consists in extracting the final color produced by the azo-dye reagent with small volumes of butyl alcohol. The method is easily applicable to routine blood analyses.

These authors worked with solutions of sulfanilamide, sulfathiazole and sulfapyridine at concentrations ranging from 0.1 to 0.5 mg. per 100 cc. After the production of the color in the usual manner, they extracted this dye with *n*-butanol. In this way they were able to concentrate the dye and so to increase the intensity of the color produced for a given amount of the bacteriostatic concerned. In the case of sulfanilamide itself, only 90 per cent of the dye was extracted, but in the case of the heterocyclic sulfonamides, production of the color was complete.

This refinement will be useful in studying bacteriostatics that are effective at low concentrations and in studying the distribution of bacteriostatics throughout various body fluids. The principle may also be used in preparing standards for direct visual comparison, as in clinical tests.

In applying this method to various primary aryl amines, it is necessary in each case to use the pure compound in question in the standard. The use of a green filter (Corning, Sextant 63, No. 401, 2 mm. thick) is desirable, especially with weak colors. The routine procedure for oxalated blood as extensively practiced in clinical laboratories calls for 2 cc. of blood. The classic procedure, in brief, is as follows:

> Exactly 2 cc. of oxalated blood is delivered into a flask and laked with 30 cc. of saponin solution. After standing for two minutes the blood proteins are precipitated with 8 cc. of 15 per cent trichloracetic acid in aqueous solution, and the precipitate is filtered off. Ten cubic centimeters of the filtrate is taken for determination of the free drug. To this sample 1 cc. of 0.1 per cent sodium nitrite is added, and the combined solution is allowed to stand for three minutes at 0° C. or at some known temperature. Next, 1 cc. of a 0.5 per cent ammonium sulfamate solution is added to exhaust the excess of nitrite. After two minutes, 1 cc. of the solution of *N*-(1-naphthyl) ethylenediamine dihydrochloride is added. The color develops rapidly.

The newer method of Bratton and Marshall,[7,8] which employs *N*-(1-naphthyl) ethylenediamine dihydrochloride, has now been adapted to the following sulfonamide derivatives: sulfanilamide, sulfapyridine, sulfathiazole, sulfaguanidine and sulfadiazine. For use with sulfamerazine and other compounds, certain modifications are necessary, but these are not yet standardized. The unknown is compared with an appropriate standard that has been treated as described above. It is convenient to set the 1-mg. (per 100 cc.) standard at 10 mm., the 0.5-mg. standard at 15 mm., and the 0.2-mg. standard at 20 mm. depth in the Duboscq colorimeter. This comparison can be made immediately, and if solutions are kept in the dark, no change in color is observed for an hour or more. To determine the total drug, 10 cc. of the filtrate is treated with 0.5 cc. of 4 N hydrochloric acid, heated in a boiling water bath for one hour and cooled, and the volume is adjusted to 10 cc. The subsequent procedure is as stated above for determining the free drug.

If the urine is used as a rough indication of blood concentration, it should be acidified and diluted so that the final concentration is 1 or 2 mg. per 100 cc. The diluted urine can then be compared with the usual standard solutions for blood, as described by Bratton and Marshall.

Atabrine* in Blood, Body Fluids and Urine

The present restrictions on methodology in the use of antimalarials — restrictions that apply even to the simplest of almost self-evident facts — prevent any detailed discussion of the aims that are to be desired in the use of atabrine, either in the suppression or the treatment of malaria. One can only quote material published in the general literature, such as the following:

> Information on the plasma concentrations of atabrine in either of the latter conditions should prove as helpful in the quantitative control of such therapy as is information on the plasma concentration of the sulfonamides in the control of sulfonamide therapy.[9]

One is not allowed to divulge the concentrations required to produce effective therapy or suppression, but one does note from the published literature that the available methods are applicable when the concentration is at least 50 microgm. per liter and the

*Although the term "atabrine" has been superseded in the *United States Pharmacopoeia XII* by the term "quinacrine hydrochloride," the older term has been retained in this article because of its general contemporary use.

amount of the aliquot contained in the sample is over 0.5 microgm. Apparently, other methods are used when the concentrations in blood or body fluids are lower than that just described.

Atabrine in blood and body fluids. One of the most useful of the methods suggested is that of Brodie and Udenfriend.[9] In this procedure, atabrine is isolated from the biologic material being investigated by extraction of the free base at a pH of about 8.0 with ethylene dichloride. The solution is washed free of the degradation products of atabrine with 2.5 N sodium hydroxide. The atabrine is then extracted in aqueous concentrated lactic acid. The final determination of the atabrine is performed in the lactic acid by means of its fluorescence.

A simpler method involves estimation of the atabrine through its fluorescence in the original ethylene dichloride solution. Incidentally, it should be remembered that this solvent may prove toxic. This last procedure is recommended for routine clinical use, and is extremely simple and rapid. In this way, even under field conditions, it is possible to know the concentrations of the drug circulating in the blood of each patient.

A similar method suggested by Masen[10] is as follows:

> Five cubic centimeters of oxalated blood is mixed with 3 cc. of 4 N sodium hydroxide and 8 cc. of an alcoholic mixture consisting of equal parts of isobutyl and isopropyl alcohol. One cubic centimeter of water and 7 cc. of petroleum ether (B.P. 30-60°C.) are added. Next, 1 cc. of the atabrine standard, containing 63.6 mg. per liter, is added to another 5-cc. sample of the same blood. It is treated similarly and is shaken for five minutes.
>
> The upper alcoholic layer containing the atabrine is removed. Preliminary centrifugation may be needed to break emulsions at this stage. To the upper layer is added 10 cc. of a solution containing 30 per cent isopropyl alcohol in 10 N hydrochloric acid. The lower layer from this combination is saved, and an 8-cc. sample is taken. This is stabilized with 1 cc. of a buffer consisting of 4 gm. of sodium borate in 100 cc. of 1.35 N sodium hydroxide. The final comparison between standard and unknown is made in a fluorometer, according to the following equation:
>
> $$\text{Conc. of unknown (mg. per liter)} = \frac{U}{S} \times \text{standard conc.} \times 200,$$
>
> U being the reading of the unknown and S, that of the standard.

The fluorometric method for estimating atabrine has been extended by Auerbach and Eckert[11] by the use of caffeine sodium benzoate. In the presence of this reagent the fluorescence of atabrine is intensified some fifteen times. With this procedure a 5-cc. sample of blood containing 0.1 microgm. of atabrine yields a significant result. Furthermore, the sensitivity is adequate for the analysis of blood concentrations such as are found under actual therapeutic conditions. A preliminary extraction with ether is required. For best results the temperature must be controlled.

This procedure has been applied to human blood and bloods from the following animals: rabbit, rat, dog and duck. At a concentration of about 4.0 microgm. per 100 cc. of whole blood, the recovery is 96 per cent or better, and the manipulation involved is simple.

Atabrine in urine. It is well recognized that after the administration of atabrine, the urine contains material that emits an intense yellow color and fluorescence. It has been assumed by some workers that this appearance of the urine is entirely due to unchanged atabrine, and this material *in toto* has been determined as a means of measuring the saturation of atabrine in the blood and body tissues. The work of Scudi and Jelinek,[12] however, has shown that a number of acridine derivatives appear in the urine following administration of the drug to experimental animals. The partition of these various acridines varies from species to species, and is different in laboratory animals from what it is in man. Consequently, any method that is to be applied clinically must take cognizance of the fact that the urinary excretion of atabrine is quite complex.[13] If the excretion products found in the urine were active against malaria, there might not be any objection to treating them as atabrine. Experiments by Seeler,[14] however, have shown that at least one of these fractions is not active against the schizonts of avian malaria at dosages of 20 to 100 mg. per kilogram. Moreover, these concentrates were more toxic than is atabrine.

The method of Brodie and Udenfriend[9] has the advantage that any decomposition products of atabrine that may also be present are not recorded. In this respect the method is preferable to somewhat simpler methods, such as that of Craig,[15] which also depends on fluorescent material. The use of fluorescence to detect the atabrines endows the procedure with a high degree of specificity. A Coleman glass filter No. B_2, combining both Corning No. 5113 (2 mm.) and No. 3389 (2 mm.), is used to limit the transmission of fluorescent light, and is more specific than Corning No. 5113 alone, which permits greater sensitivity but transmits a considerable amount of fluorescence derived from normal components of biologic materials.

Quinine in Blood, Body Fluids and Urine

Now that many observers have decided that quinine is *not* the drug of choice in many cases of malaria, information regarding its pharmacologic fate is being released for general perusal. Intensive work on its behavior in animals and man has been accumulating behind closed doors during the last three years, and some of it — especially work on the related isomer quinidine — will be of permanent and practical interest. Of this large and rapidly appearing literature, only a few significant instances can be cited.

Quinine in blood and body fluids. In 1931, Vedder and Masen[16] demonstrated that the effectiveness of antimalarial therapy depends on the maintenance of certain concentrations of the drug in the circulation. Because the drug disappears rapidly from the blood after intravenous injection,[17, 18] it is desirable to follow the blood level to ascertain the need for

further dosage or to regulate the program of medication. Until recently highly specific methods were available, but these generally involved a time-consuming extraction process. Brodie and Udenfriend,[19] however, have described a simple but precise method probably applicable to human plasma.

The test is based on the strong fluorescence of acid solutions of the alkaloid in ultraviolet light. When the quinine concentration is low, the intensity of emitted light is proportional to the alkaloidal concentration. The absolute concentration is, in fact, too low because of so-called "quenching," but this fault is automatically corrected by using appropriate control standard solutions. In order to avoid serious loss of the drug by adsorption on the protein precipitate, the plasma filtrates are prepared at high dilution by the use of metaphosphoric acid. The final concentration is read in a photofluorometer over the range of 1 to 30 microgm. per 100 cc. Above plasma concentrations of 100 microgm., the method gives very satisfactory results. Moreover, because the filtrates are stable, they can be stored for several days and analyzed in groups. The method is also adaptable to quinidine.

In connection with experimental work on avian malaria, Kelsey, Oldham and Geiling [20] have studied the distribution of quinine in the tissues as well as in the blood of fowls after oral administration. These results were compared with the effect of intravenous injection. An interesting finding was a temporary accumulation of quinine in the red cells at a concentration higher than that in plasma. The leukocytes show an even more striking preferential accumulation. The blood rapidly yields up its initial load of drug, so that ten minutes after intravenous injection high concentrations are found in the liver, kidneys, spleen, adrenal glands, lungs and liver. The data serve to emphasize the important fact that quinine is not accumulated in the tissues even after long-continued administration. Quantitatively, the results confirm those in the dog and cat reported by Hatcher and Weiss.[21]

Quinine in urine. The medical services of the armed forces have been obliged to develop simple tests for the detection and rough estimation of quinine in the urine. Such tests are needed to detect those who have failed to take prophylactic medication. They may also be used in a semiquantitative fashion to control suppressive dosage. Independent studies by Cornell and Kaye[22] and by Glazko[23] have shown that the double iodide of mercury (HgI_4K_2) can be used directly in urine without preliminary extraction. The precipitate of iodomercurate dissolves on boiling, whereas albuminous precipitates do not. If precise results are needed, the turbidity produced can be measured with a photonephelometer. In this case the acidity and the range of concentration of the quinine must be adjusted for best results to pH 2.0 and 1 to 5 mg. per 100 cc., respectively. When 0.6 gm. of quinine sulfate was ingested, it was found by this method that the urinary quinine excretion rose at four hours to a peak of nearly 25 mg. an hour, and gradually declined to less than 5 mg. after fourteen hours.

Although urinary quinine excretion is variable, approximately 40 per cent of the usual therapeutic dosage is excreted by this route. The excretion is rapid, and after twenty-four hours only a trace appears in the urine.

The excretion of quinine is influenced by several variables, among which the urinary acidity is important. Haag, Larson and Schwartz,[24] for example, gave 0.5 gm. of quinine orally to human subjects and found that when the urine was maintained alkaline, half as much quinine was excreted as with an acid urine. At best, however, the resulting conservation of the drug seemed to be less than 10 per cent.

Penicillin in Blood and Body Fluids

In the use of penicillin it is especially advantageous to determine the concentration of circulating antibiotic, particularly in cases being used for statistical studies of the therapeutic results. Penicillin is so rapidly removed from the blood stream and so largely excreted in the urine that an interval of two hours reduces the effective concentration to very low limits.

Some 58 per cent of penicillin is excreted by the kidneys after intravenous injection.[25] Rammelkamp and Keefer[26] found that this loss occurs largely in the first hour after injection. The effect of Diodrast in preventing the excretion was striking. Whereas about 57 per cent of intravenous penicillin was lost in the course of a few hours, with Diodrast only 32 per cent was recovered in the urine. Despite this conservation of penicillin, however, the blood level became negligible in less than two hours. Without Diodrast, it reached zero in approximately forty-five minutes.

The hemolytic streptococcus is extremely sensitive to penicillin, but even in this instance a concentration of at least 0.15 units per cc. is desirable. Various procedures and various derivatives are being tested in the hope of maintaining a high concentration over a longer period. At present the drug must be administered every two hours in order to hold the blood concentration up to effective levels.

The methods now available for the estimation of penicillin activity are essentially bioassay procedures. Accordingly they involve the usual *bête noire* of biologic variation. This fact implies that for greatest accuracy the answer, in graphic terms, should be read as a *line* rather than as a single point or single value. The new methods for the assay of penicillin take cognizance of this statistical situation, and provide for a matching of the unknown with known standards. Unfortunately no extensive published experience is yet available with this type of procedure as applied to blood.

One of the most convenient of these newer procedures is that of Sherwood, Falco and de Beer.[27] The authors have informed me that it should prove satisfactory for blood provided the standard dilutions of penicillin (used for comparison) also contain an equivalent amount of blood. In this method, 25 cc. of nutrient agar (pH 7.0) containing 200,000 *Bacillus subtilis* spores per cubic centimeter is poured into a Petri dish, and after the agar has solidified, four sterile filter-paper disks (15.3 millimeters in diameter) are spaced evenly upon its surface. These disks are used to absorb and retain the samples under test. Four plates are employed, each testing simultaneously two dilutions of the standard (S) and two of the unknown (U). The weaker of both dilutions should be one fourth as concentrated as the stronger. Each of these four samples is placed on one of the paper disks and allowed to soak into it. In taking small samples of the four liquids, it was found that a bacteriologic loop was nearly as accurate as a micropipette. The loop had the advantage that it was more readily cleaned and prepared for use. After some five hours of incubation at 37°C., the colonies of *B. subtilis* should have grown sufficiently to delineate clear zones of inhibition. The diameter of this zone should be measured to the nearest millimeter, and the sums of the four zones of inhibition produced by the standard (S_1) and weak standard (S_2) and by the unknown (U_1) and weak unknown (U_2) should be ascertained by addition.

The potency of the unknown (U) with reference to the standard (S) can be calculated from the following equation,

$$\text{Potency} = \text{antilog} \left\{ 2 + d \frac{(U_2 + U_1) - (S_2 + S_1)}{(U_2 - U_1) + (S_2 - S_1)} \right\}.$$

In this equation, d signifies the log of the ratio of the greater dose to the smaller dose. This type of assay is statistically sound and convenient. It deserves a careful trial with blood and other body fluids.

In applying this method, it is necessary to control a number of variables that affect the answer. Among these are the temperature and duration of incubation, the size of the disk, the depth of the agar, the volume of the dose and the number of *B. subtilis* spores per plate. If these factors are maintained constant, however, the results are satisfactory for most biologic problems.

Recently Goth and Bush[28] have suggested a rapid method for the estimation of penicillin. This is based on the finding that the antibiotic inhibits the production of nitrite from nitrate by cultures of *Staphylococcus aureus*. This test can be carried out in less than ninety minutes. Furthermore, its accuracy is greater than that of the serial dilution method commonly used.

The test strain of *Staphylococcus aureus* is grown for twenty-four hours in a special peptone medium and then diluted with a medium containing peptone, sodium nitrate and *p*-aminobenzoic acid. A standard preparation of penicillin is used as a control tube and treated in the same fashion as the unknown. After sixty to ninety minutes' incubation the concentration of nitrite is determined.

The determination of the nitrite formed is based on the method of Shinn.[29] A trichloracetic acid filtrate is treated with *N*-(1-naphthyl)ethylenediamine dihydrochloride. The resulting color is determined after three minutes in a photoelectric colorimeter with a green filter (Cenco No. 525P). Because an excess of *p*-aminobenzoic acid is present, the intensity of the color developed in this diazotization process is determined by the concentration of the nitrite present. Appropriate standard solutions containing known concentrations of nitrate are used as the basis for comparing the control tube with the unknown. Obviously, it is essential that all cultures be incubated for the same time at the same temperature.

Rammelkamp[30] has also described a simple method for determining the concentration of penicillin in body fluids and exudates. Because hemolytic streptococci are four to sixteen times as sensitive as staphylococci, an especially sensitive Group A strain of hemolytic streptococcus isolated from a case of erysipelas was chosen. Broth cultures at twelve hours (in veal infusion with 1 per cent erythrocytes) were diluted so that the number of organisms per cubic centimeter ranged from one thousand to ten thousand. Half a cubic centimeter of this dilution was added to each unknown sample, comprising 0.7 cc. total volume. The test tubes were then incubated for eighteen hours and finally examined for hemolysis. By comparing such a series with a series containing known amounts of penicillin, one can estimate amounts as low as 0.0039 Florey unit per 0.2 cc. of solution.

This method is applicable to urine, whole blood, erythrocytes, joint fluid, spinal fluid and exudates from empyema cavities. Unknown samples may be stored at 5°C. for two weeks before testing without serious loss, unless contaminated. In such a case it is wise to sterilize the sample by passage through a Berkefeld or Seitz filter.

Effective concentration. Rammelkamp and Keefer[26] studied the concentrations of penicillin in the blood stream required to produce optimal effects. For *Streptococcus haemolyticus* the value was between 0.019 and 0.156 unit per cubic centimeter of serum, whereas for maximum bacteriostatic effect with *Staph. aureus*, at least 0.156 unit was required. Furthermore, whole blood containing 5.1 mg. of sulfadiazine per 100 cc. was less active against streptococci than was whole blood containing 0.7 unit of penicillin per 100 cc. After intravenous (or intramuscular) injection of penicillin large amounts of the drug appear in the urine, even as much as half the injected material. Unfortunately, intravenous injection is not followed by elimination of penicillin

into the spinal fluid. It has been assumed that for this reason penicillin administered intravenously is useless in the treatment of meningitis.

Recent work by Rosenberg and Sylvester,[31] however, has indicated that the blood-brain barrier is altered in cases of meningitis. These investigators injected 8 patients with meningitis intravenously or intramuscularly, in doses ranging from 20,000 to 40,000 Oxford units. One or two hours later penicillin appeared in the spinal fluid in concentrations of 0.03 to 0.35 unit per cubic centimeter. Because the magnitude of this concentration is adequate for blood, the possibility exists that such cases can be treated without intrathecal injection. Further data are needed. Such observations should, of course, be made only under carefully controlled circumstances, but they appear to show that observations in normal subjects do not reflect the situation when inflammation is present.

Various devices are now under test in an effort to maintain effective concentrations of penicillin for longer periods. Some of these involve a modification of the preparation of penicillin, but these experiments are still in the initial stages so far as information is available at present. Another interesting approach, however, has been the depression of renal excretion by agents that are relatively innocuous to the kidney. For example, Rammelkamp and Bradley[26] found that the excretion of penicillin by the kidney was inhibited after the injection of Diodrast.

Recently Beyer and his associates[32] have investigated a similar use of *p*-aminohippuric acid, which is secreted by the tubular epithelium, as shown by Smith and his associates[33] and by Bing.[34] Experiments in dogs conducted by Beyer and his associates showed that when the plasma level of the hippuric acid derivative is maintained at between 20 and 30 mg. per 100 cc., penicillin is retained in the blood at effective concentrations for appreciably longer periods. Thus, in the control experiments after a single injection of 10,000 Oxford units, the antibiotic was no longer detectable in the plasma after two and a half hours. In animals treated with the hippuric acid derivative, however, detectable concentrations of penicillin persisted in the plasma for three and a half hours. Simultaneously the renal clearance of penicillin from the blood and its recovery in the urine were decreased. Toxicologic studies have shown in mice, rabbits and dogs that *p*-aminohippuric acid is remarkably nontoxic, so that a cautious trial of its use with penicillin is desirable in view of the higher concentrations possible and the increased economy of therapy.

The methodologic aspect of controlled chemotherapy has been stressed in this survey because it is too often neglected. Any clinical report is of little scientific value if it claims that penicillin is ineffective without giving evidence that the concentration in the circulating blood has been maintained adequately high and for an adequately long period. At this stage of knowledge regarding penicillin and other antibiotics, the necessity for constant control of concentration in the blood cannot be emphasized too strongly.

Summary

If the antibiotics and bacteriostatic agents now available are to be used effectively, their circulating concentration must be known and controlled. Simple methods are now available that can be applied to blood, urine and body fluids. Unless such a check is used in critical cases, it is unwarranted to conclude that the therapeutic agent under test is ineffective. This precautionary procedure is also necessary in most cases to guard against toxicity due to overdosage.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 30451

PRESENTATION OF CASE

First admission. A seven-year-old Negro schoolgirl entered the hospital because of exophthalmos. The child had been in apparent good health until fifteen months before entry, when she seemed to become restless, nervous, irritable and emotional. A month or two later exophthalmos was noted. During the next few months the symptoms progressed, becoming more marked after an attack of measles. She failed to gain weight, although there was an increase in height of 2 inches in six months. About one month before entry, during an examination in a community hospital, a lump was found in her neck and the basal metabolic rate was noted to be +65 per cent.

The patient had had whooping cough at four years of age and chicken pox shortly afterward. There was a question of head injury at fifteen months of age but x-ray films of the skull taken at a community hospital at that time were negative.

Physical examination showed a well-developed and well-nourished girl. There was slight tremor of the tongue. The thyroid gland was symmetrically and uniformly enlarged. No thrills were palpable over the gland, but a bruit could be heard. Exophthalmos was present, and the hands showed a moderately coarse tremor. There was a loud systolic murmur, best heard at the apex but audible over the entire precordium.

The blood pressure was 120 systolic, 60 diastolic. The temperature was 99°F., the pulse 120, and the respirations 25.

Examination of the blood showed a red-cell count of 5,100,000, with 85 per cent hemoglobin. The white-cell count was 7500, with 74 per cent neutrophils. The urine was normal, with a specific gravity of 1.026. The basal metabolic rate was +63 per cent. The serum cholesterol was 127 mg. per 100 cc. A blood Hinton test was negative.

The patient was given 1 drop of a saturated solution of potassium iodide three times a day, and on the twentieth hospital day a right hemithyroidectomy was performed. The weight of the specimen was 8.2 gm., and on microscopic examination it showed hyperplasia. The patient withstood the operation well, but on the first and third postoperative days there was considerable oozing of blood from the incision and she was given several transfusions. On the fourteenth hospital day the basal metabolic rate was +15 per cent for height and +32 per cent for weight, with a pulse of 96. The patient was discharged on 5 drops of potassium iodide twice a day and was told to return in six weeks for the removal of the remaining lobe of the thyroid gland.

Second admission (six weeks later). Following discharge the patient remained well, gained 10 pounds and was less nervous.

Physical examination was the same as before.

The temperature and respirations were normal, and the pulse was 96. The basal metabolic rate was +43 per cent for height and +54 per cent for weight.

On the second hospital day a left hemithyroidectomy was performed with the removal of 15 gm. of histologically hyperplastic thyroid tissue. Again there was considerable postoperative bleeding. The basal metabolic rate fell to +5 per cent, and the pulse to 78, and she was discharged on the tenth hospital day.

Final admission (eight years later). Following discharge the patient did well for about two years, at the end of which time definite thyroid tissue was again palpable in the neck and seemed to be increasing in size. The basal metabolic rate was +16 per cent for height and +30 per cent for weight, and the pulse was 120. She was placed on 5 drops of a saturated solution of potassium iodide three times a day. During the next two years, tremor and nervousness reappeared, the mass in the region of the thyroid gland definitely enlarged and the basal metabolic rate rose to +23 per cent for height and +34 per cent for weight. At that time she was given 150 r of x-ray therapy for two doses, followed by two doses of 200 r each. During the month after x-ray therapy the basal metabolic rate gradually fell to −17 per cent for height and −13 per cent for weight; the pulse was 66. She then developed a rash and the potassium iodide therapy was discontinued. The thyroid nodule decreased in size and her condition seemed much improved. The patient apparently remained well until three weeks before the final entry, at which time her appetite became poor and she developed polyuria and polydipsia, and began to lose weight. Ten days before entry she appeared tired, "pepless" and sleepy and complained of pain and tenderness in the costovertebral angles. One week prior to admission there was itching of the genitalia and anus, followed by the draining of a perianal "abscess" three days later. Two short episodes of epistaxis occurred spontaneously. The night before entry the patient became drowsy, with frequent attacks of vomiting, and the next morning was difficult to rouse.

*On leave of absence.

Physical examination showed a semicomatose, dehydrated girl with typical Kussmaul respirations at a rate of 45. Considerable tenderness was present in both costovertebral angles. A draining abscess was present on each side of the anus; both, however, appeared to be quite superficial. Examination was otherwise negative.

The blood pressure was 130 systolic, 70 diastolic. The temperature was 102°F., the pulse 140, and the respirations 45.

Examination of the blood showed a red-cell count of 5,140,000, with 15 gm. of hemoglobin. The white-cell count was 35,500, with 84 per cent neutrophils. Examination of the urine showed a specific gravity of 1.020, a reaction of pH 6, a + test for albumin, a red test for sugar, a ++++ test for diacetic acid and a ++++ test for acetone; the sediment contained 10 to 15 red cells and 50 to 60 white cells per high-power field. The blood sugar was 500 mg. per 100 cc., and the carbon dioxide combining power 5.7 millimols per liter.

Over the next two hours the patient was given 150 units of insulin subcutaneously and 300 units intravenously in divided doses, with the result that the blood sugar dropped from 500 to 330 mg., the test for sugar in the urine changed from red to brown and the acetone became noticeably less (+++). Over the next four hours the test for sugar in the urine changed to green, with a + test for acetone. Only 80 units of insulin were given subcutaneously over that period of time. During the first six hours she received intravenously 4500 cc. of a solution consisting of two-thirds isotonic saline solution and one third 1/6 molar sodium lactate solution, as well as 250 cc. of plasma. At the end of that period the urine showed only a faint test for acetone and a negative test for sugar. She was more responsive, and the respirations were 35 and approximately normal in depth. The measured urine output during that period was 1560 cc., but it actually was greater since a considerable amount leaked around the catheter.

On admission 1000 cc. of clear fluid had been aspirated from the stomach; the tube was left in place, and the viscus was kept empty by frequent aspirations. At the end of five hours 25 cc. of broth was introduced through the tube into the stomach; this was repeated at half-hour intervals and was well tolerated. The perirectal abscesses were opened, about 20 cc. of pus being obtained. The patient was then given 1000 cc. of 10 per cent dextrose in isotonic saline solution, along with 40 units of insulin, over one and a half hours. The test for urine sugar, however, was brown, and that for acetone +++. At that point the patient became less responsive and the respirations assumed a peculiar gasping quality. Isotonic saline solution containing 2.5 gm. of sodium sulfadiazine was given intravenously because of persistent leukocytosis and a fever of 101°F.; the volume was 2000 cc. over the next five hours, making a total of 6850 cc. of parenteral fluids. The urine output continued to be approximately 200 cc. per hour. The insulin dosage was between 30 and 60 units an hour from the eighth to the twelfth hour of hospital stay, at which time the test for urine sugar became negative. Subsequently only small doses of insulin were introduced, the total dosage of regular insulin being 810 units. The patient became acetone free from the tenth hour on.

Gasping respirations continued, however, and the patient remained semiresponsive. The blood pressure was constant at 130 systolic, 70 diastolic, except for occasional transient rises to 150 systolic, 70 diastolic; one and a half hours before death it rose to 160 systolic, 100 diastolic. The pulse never dropped below 120. At no time was peripheral or pulmonary edema evident. The white-cell count varied from 27,000 to 29,000. Sixteen hours after entry the patient suddenly became unresponsive, and expired fifteen minutes later.

Differential Diagnosis

Dr. Allan M. Butler: This is an example of hyperthyroidism in childhood, which is frequently extremely serious. Because hyperthyroidism in childhood is so rare, and since most pediatricians know so little about the condition, when they encounter a case of hyperthyroidism they had better send it to a physician for adults who knows hyperthyroidism rather than attempt to treat the case themselves.

I shall start discussing this case at the third admission, eight years after the original admission. The patient was then fifteen years of age. At that time she again had a recurrence of the symptoms of hyperthyroidism in spite of two subtotal thyroidectomies. The decision was made to irradiate the thyroid gland, following which the manifestations of the hyperthyroidism disappeared. Since we are not told much else about the child's thyroid condition, I assume that there were no further symptoms of hypothyroidism.

The development of polydipsia, polyuria, loss of weight and change in appetite usually means one of three things — renal disease, diabetes mellitus or diabetes insipidus, with or without brain tumor. It may possibly mean Addison's disease.

I should like to know whether the child was constipated.

Dr. George C. Cotzias: She was not constipated.

Dr. Butler: Usually with dehydration resulting from untreated diabetes, the patient becomes constipated. Abdominal pain, probably due to the dry, impacted feces that result from dehydration and constipation, is not uncommon. But this patient was not constipated, and the pain and tenderness were in the costovertebral angle according to the record — not in the abdomen. Is that correct?

Dr. Cotzias: Yes.

DR. BUTLER: One can have local irritation resulting from glycosuria. I have never seen perianal abscesses in children with diabetes. I do not know whether or not they occur in adults.

The epistaxis makes one wonder whether there was a generalized infection, hypertension or rheumatic fever. I do not recall epistaxis in diabetes insipidus, in diabetes mellitus or in Addison's disease.

Tenderness in the costovertebral angle was again definitely elicited on physical examination. I should like to know how well or poorly this patient was nourished.

DR. COTZIAS: She was well nourished.

DR. BUTLER: The draining perianal abscesses on entry apparently were not superficial, since pus was obtained on incision. One wonders whether a tuberculin test was done.

DR. COTZIAS: Not during the time that we saw her.

DR. BUTLER: There was no evidence of infection, other than these abscesses in the perianal region.

Are there any other records of blood pressure? There is no evidence that she had a hypertension preceding the dehydration.

DR. COTZIAS: I do not recall.

DR. BUTLER: If a person with diabetes mellitus cannot ingest food, the resulting starvation leads to an overproduction of ketone bodies and acidosis develops rapidly. If such a person then begins to vomit, the combination of glycosuria, ketosis and loss of fluid by vomiting quickly produces dehydration. In the presence of such dehydration the hands and feet are usually cold, the circulation poor, and the temperature not elevated, but the last frequently becomes elevated as the patient is hydrated. Hence, the temperature of 102°F. on admission suggests infection. The pulse was 140. One wonders whether the pulse was poor and thready.

DR. COTZIAS: The pulse was poor.

DR. BUTLER: That probably reflected the dehydration, possibly an overwhelming infection. The respirations were 45 and Kussmaul in character.

"Examination of the blood showed a red-cell count of 5,140,000, with 15 gm. of hemoglobin." Severe dehydration may produce a normal red-cell count when actually there is anemia. The white-cell count was 35,000. That is high but not impossibly high for just dehydration. It does, however, make me think of infection.

I imagine the urine examination was done on a catheter specimen. We have to assume that there was real albuminuria and that it was not just from the vulval contamination of a voided specimen. The white cells may reflect a cystitis. The blood sugar was 500 mg. per 100 cc., which is average for diabetic coma. I take it that no casts were seen, which is against nephritis.

A positive story, positive physical findings, an elevated blood sugar and positive tests for urine sugar, diacetic acid and acetone in a dehydrated patient indicate diabetic acidosis. Kussmaul breathing confirms the suggested metabolic acidosis.[1] It tells one that the blood carbon dioxide content is low. I suggest that a whole blood or serum carbon dioxide determination in such a patient is relatively uninformative.[1]

Suppose this child had salicylate poisoning instead of diabetes mellitus and diabetic coma. Then the hyperventilation would have been due to the toxic action of the salicylates on the respiratory center; the carbon dioxide content would still have been low, — perhaps not this low, — but the patient would have had an alkalosis, not an acidosis.[1] So the carbon dioxide determination does not even tell whether the patient had acidosis or alkalosis, unless one has used one's common sense as regards the history and physical findings. When one has done so, a carbon dioxide determination contributes practically nothing. Even in a quantitative sense it adds little of clinical importance, since the Kussmaul breathing indicates the extent of the acidosis.

So I should not have asked for a carbon dioxide determination. But I should have asked for a nonprotein nitrogen test, since this child possibly had renal disease, and I think that her care in the next twenty-four hours would have been facilitated if it was known whether or not she had renal disease. A high nonprotein nitrogen level on admission might merely have been due to the dehydration. But after the child was hydrated and a good urine volume was obtained, a second test would have shown the part that renal disease played in the picture. I should also rather have had a serum protein than a serum carbon dioxide, because the patient was sure to be given a lot of parenteral fluids. The concentration of the serum protein would have provided information concerning the patient's nutritional state and her ability to handle parenteral fluids. If the serum protein was elevated, fluids could have been given parenterally without danger of edema unless there was a lot of infection. If the serum protein concentration was not elevated in the state of dehydration, one could have been sure that it would be lower after hydration and hence would have been careful about edema as parenteral fluids were given.

I am going to pass over the insulin therapy. I do not believe that the amount of insulin given is really the important factor. One should give enough and not too much. The main thing is the manner in which this patient was supplied with the immediate metabolic needs of fluid and with other substances, including insulin. In the first two hours of therapy the blood sugar fell from 500 to 330 mg., and the acetone was somewhat less, perhaps because all the urine analyses were qualitative — not only in terms of chemistry but in terms of urine volume. I am sure that when the tests for acetone and sugar were done no account

was kept of the relation of the qualitative tests to the quantity of the urine. Hence, all were qualitative.

The acetone determination warrants one comment. A patient in recovery from diabetic coma should not become free of glycosuria before the ketonuria has been cleared up. The persistence of ketosis means the continuation of starvation, which is the cause of the ketosis. The ketosis is a factor in the diabetic acidosis, nausea, dehydration, and so forth. The starvation must be corrected before the ketosis can be stopped, and the only means of stopping starvation early in treatment is the administration of glucose with adequate insulin. Hence, enough glucose should be given so that the urine does not become sugar free until the ketosis has stopped.

"During the first six hours she received intravenously 4500 cc. of a solution consisting of two-thirds isotonic saline solution and one-third 1/6 molar sodium lactate solution, as well as 250 cc. of plasma." That solution, in my estimation, is the correct solution to give in the early stage of repairing the extracellular fluid loss in diabetic coma.[1] The concentration of sodium chloride and lactate (or potential bicarbonate) in such a mixture prevents the continuation of the acidosis while hydrating a patient who is so dehydrated that the kidneys will not function correctly. If one gives physiologic saline solution instead of this combination of two solutions one is administering a solution that, in terms of serum, is hypertonic in chloride by 50 milliequiv. per liter.[1] Physiologic saline solution also has no bicarbonate. The result of giving physiologic saline solution to a patient whose kidneys are handicapped by the poor blood flow incident to dehydration is an elevation of serum chloride and a continuation of the acidosis. To continue for hours the Kussmaul breathing and resultant muscular exertion in a diabetic patient who has suffered severe starvation, severe dehydration and severe cardiac and circulatory embarrassment is not good therapy. The particular combination of sodium lactate and saline solutions is good because it provides an approximately normal plasma chloride concentration — 100 milliequiv. per liter — and a bicarbonate or potential bicarbonate (according to whether one uses sodium bicarbonate or sodium lactate) concentration of approximately 50 milliequiv. per liter, which is double the normal. So immediately there begins a correction of the alkalosis; almost immediately the respirations improve, and in an hour they will be rather markedly improved. Such an infusion cannot do harm. If it puts the patient to rest, it must be good. As soon as the respirations are eased, physiologic saline solution can be used in place of the combined solution.

I am not sure that the disappearance of sugar from the urine meant that the blood sugar had returned to normal, for this patient may have had renal disease and a hyperglycemia without glycosuria. Whether or not she had renal disease, I should have favored using intravenous glucose after a couple of hours of hydration therapy, since the maintenance of hyperglycemia favors the utilization of glucose and starvation can be stopped only if there is a utilization of glucose. The work of Mirsky[2] shows that hyperglycemia improves the utilization of glucose. There is no evidence that maintaining the blood sugar above normal does harm provided that something is done about hydrating the patient and that the urine volume is adequate, as it was in this patient. Thus, after two hours of therapy 5 per cent glucose might have been started intravenously, later increasing the glucose to 10 per cent and using insulin in liberal doses while giving the glucose. Glucose administered beyond the rate of immediate oxidative utilization builds up the depleted glycogen stores. Unless this is done, the high blood sugar and the ketosis are difficult to control.

There were no signs or symptoms of pulmonary edema or cardiac failure during the parenteral therapy, since the rate and volume were not excessive.[1] Yet this patient died in the same manner that patients with diabetes sometimes do; that is, after considerable hours of therapy and improvement, they suddenly fail rapidly and die. Analyses show that the serum sodium, chloride and carbon dioxide and the blood sugar were satisfactory. The urine sugar and ketosis had cleared up. Yet she died. I do not know why, but possibly Dr. Castleman can tell us. In this particular case a renal infection or a pre-existing nephritis may have been a factor. Because there is no record of urine cultures and nonprotein nitrogen determinations and because of the presence of perianal infection I do not know whether there was renal infection or nephritis.

In the interest of possibly improving the treatment of such patients, attention should be called to the fact that for sixteen hours this starving patient was given nothing but water, sodium chloride, glucose and insulin, with the exception of a few ounces of meat broth. Extracellular fluid and a total of only 100 gm. of glucose, providing 400 calories, were given this depleted patient. Possibly another 90 gm. of glucose from the body was oxidized to provide an additional 360 calories, but no intracellular constituents were given with these 760 calories to provide for cellular activity or repair. Such is the custom. It ignores the fact that extracellular repair does not restore intracellular depletion, nor does it provide substances essential to the life of cells and patients.

DR. BENJAMIN CASTLEMAN: Dr. Lerman, would you like to say something about the relation of diabetes to exophthalmic goiter.

DR. JACOB LERMAN: Presumably this child did not have diabetes at the time she was treated for

hyperthyroidism, although she may have had a mild degree. We have seen older people who have a high degree of diabetes with hyperthyroidism. Whereas this patient had a fairly severe diabetes, I am wondering if she did not have persistent hyperthyroidism right through, which accounted for the sudden development of a severe grade of diabetes. Ordinarily, when a person has diabetes of mild or severe degree and hyperthyroidism, there is practically no diabetes left after the latter is cured, so that unless diabetes had been present for a long time or unless the hyperthyroidism had become worse, we have to assume that the diabetes was a new development. On the story, I should think that the patient was cured so far as the hyperthyroidism was concerned and that she developed diabetes de novo. I did not see her during the last episode.

Clinical Diagnoses

Diabetic coma.
Perirectal abscesses.

Dr. Butler's Diagnoses

Perianal abscesses.
Diabetes mellitus, with acidosis.
Intracellular depletion.
Cardiac failure.
Cystitis?
Pyelonephritis?
Nephritis?

Anatomical Diagnoses

(Diabetes mellitus.)
(Diabetic coma.)
Hydropic degeneration of islets of Langerhans of pancreas.
Lymphocytic infiltration of pancreas.
Bronchopneumonia.
Perianal abscesses.
Acute cystitis.
Pulmonary atelectasis.
(Thyrotoxicosis.)
Operative scar: thyroidectomy.

Pathological Discussion

Dr. Castleman: The last basal metabolic rate was three years before entry and was normal, being +2 per cent. Autopsies on patients with diabetes, as Dr. Butler has mentioned, are usually unsatisfactory. We are rarely able to diagnose the exact cause of death. In many cases, infection is the underlying factor that puts the patient into coma.

In this child I should think the severe perianal infection probably started the ball rolling and resulted in coma. There was a lot of perianal infection at the time of autopsy, as well as scattered foci of bronchopneumonia. We were able to get a piece of thyroid tissue, which showed no evidence of activity; the abnormal histology was perhaps due to irradiation, such as we have seen in other cases. The pancreas was about normal in size and on section showed something that I had never seen before — a fairly diffuse lymphocytic infiltration throughout the parenchyma, which for the most part did not involve the islets. Not having seen many cases of diabetes in children, I talked to Dr. Shields Warren; he also had never seen this type of lymphocytic involvement. I believe that we have to assume that it was just the result of a mild chronic pancreatitis, because in addition to that there were numerous areas of fibrosis and destruction of the acinar tissue. The islet cells themselves were about normal in size and number, but in many there was definite hydropic degeneration, the type of change that one sees in acute, severe diabetes in children. There was also a mild cystitis and pyelitis, but no evidence of kidney disease. The glycogen stains showed what we expected to find — deposits of glycogen in Henle's tubules in the kidneys and a liver almost completely replaced by glycogen.

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CASE 30452

Presentation of Case

A sixty-two-year-old housewife entered the hospital because of severe pain in the back.

So long as she could remember, the patient had experienced low back pain radiating down the posterior aspects of both legs to the heels. The pain was intermittent and lasted for days. Occasionally it occurred after lifting or carrying heavy bundles, but this was not the rule. Six months prior to entry the pain increased in intensity and frequency and was severer in the right leg than in the left. She had frequent muscle cramps in the right leg. According to one statement the pain always started on the right side, and when severe, it was also felt in the left leg. At times the pain was severe enough to require codeine. There was paresthesia of the small toe of the right foot.

Physical examination showed a moderately obese woman who experienced severe distress on motion. The heart, lungs and abdomen were normal. There was slight tenderness in the lower lumbar region. Straight leg-raising on the right was limited to 35° and produced pain down the back of the leg to the heel. On the left it was limited to 60°, with pain down the back of the leg to the knee. Forward bending was limited, and the fingertips could be brought to within only 40 cm. of the floor. The lumbar spine was moderately flattened. Jugular compression did not cause pain. The right

ankle jerk was absent, but the neurologic examination was otherwise negative.

The blood pressure was 150 systolic, 90 diastolic. The temperature, pulse and respirations were normal.

Examination of the blood showed a white-cell count of 8500. The urine was normal. A blood Hinton test was negative.

Anteroposterior and lateral films of the lumbar spine showed flattening of the lumbar curve and a list to the left between the fourth and fifth lumbar vertebras. The interspace between these vertebras was markedly narrowed, and there were degenerative changes at this level and between the fifth lumbar vertebra and the sacrum, with increased density of the margins of the vertebral bodies.

Lumbar punctures at the third and second interspinous spaces caused unusually severe pain. Only a few drops of spinal fluid were obtained. Because of the pain further attempts at lumbar puncture were not made.

On the sixth hospital day an operation was performed.

Differential Diagnosis

Dr. Jost Michelsen: At first glance this seems to be a story of a ruptured intervertebral disk in the lower lumbar region on the right side. For many years the patient had intermittent pain low in the back and in both legs, more so on the right side. The pain was severe and was exaggerated by certain activities. It occurred after lifting or carrying bundles. It was associated with paresthesia of the small toe on the right. There was limitation in forward bending. The lumbar spine was flattened. The right ankle jerk was absent. All these facts are consistent with a ruptured disk in the lower lumbar region.

I shall disregard the x-ray findings of narrowing of the fourth lumbar interspace. It may be found as an incidental observation in patients with no symptoms. The evidence of proliferative changes at the fourth and fifth interspaces is also of little significance for the diagnosis of the level of the lesion.

The paresthesia of the right small toe and the absence of the right ankle jerk indicate that the right first sacral posterior nerve root was involved. Consequently, if the lesion was a ruptured disk it was a protrusion at the lumbosacral interspace on the right side.

The question arises whether this was a ruptured disk. For several reasons I have a notion that it was not. I am inclined to believe that the severe pain that was observed during the lumbar puncture and the fact that only a few drops of cerebrospinal fluid were obtained are significant. I assume, of course, that the lumbar puncture was well executed. The pain, as well as the small amount of fluid, suggests that there was an intradural mass. On reviewing the history with this possibility in mind one gets the impression that the pain that the patient had had for so many years was not of true mechanical nature. It is said that occasionally it occurred after lifting or carrying heavy bundles, but that this was not the rule. Intermittent spells of pain lasting for only a few days would also be somewhat unusual for a ruptured disk. This is all I have to go on, however, when I suggest the possibility that the lesion was an intraspinal neoplasm.

If there was a tumor, I presume that it had been present for a long time. This is against a malignant lesion. Of other lesions, I should consider neurofibroma, meningioma and ependymoma. Meningiomas in the lumbar area are extremely rare, and I have never heard of one in this area. Ependymomas frequently occur in the cauda equina region. With the long duration of symptoms, however, one would expect widening of the spinal canal, destruction of the pedicles and erosion of the posterior portion of the vertebral bodies at the site of the lesion and probably definite signs of compression of the cauda equina. This leaves us with the third possibility, which is the likeliest. Neurofibromas are the most frequent of the neoplasms of the spinal canal. These nerve-sheath tumors vary in size. It is possible that the tumor originated from the first sacral posterior root on the right and expanded slowly to produce the cerebrospinal-fluid disturbances and displacement of nerve roots, which led to the difficulties that were encountered on lumbar puncture.

I admit that I am unable to make a definite diagnosis of the type of the lesion and only an approximate diagnosis of its true seat. I believe that the patient had an intraspinal lesion in the lumbar area, either a large ruptured disk at the lumbosacral interspace or an intradural neoplasm in the region of the cauda equina. I favor the diagnosis of a neoplasm, either an ependymoma or, likelier, a neurofibroma.

Dr. Augustus S. Rose: I was wondering if the absence of sphincter difficulty is of any significance.

Dr. Michelsen: As I tried to point out, it is particularly against an ependymoma. The lesion was probably a neurofibroma.

Dr. James B. Ayer: Is the absence of sensory findings against neurofibroma?

Dr. Michelsen: The fact that the only sensory disturbance was a paresthesia of the right little toe is extremely significant.

Dr. Charles S. Kubik: Paresthesias are of no assistance in diagnosing the nature of the lesion, but they do help to localize it.

Dr. Michelsen: That is correct.

Dr. Ayer: I admit that it is possible for a large ruptured disk lying in the canal to cause paresthesia.

DR. SAMUEL LOWIS: The fact that the patient had pain on lumbar puncture at two different levels favors tumor rather than a ruptured disk. Furthermore, a ruptured disk would not be so large as this lesion.

CLINICAL DIAGNOSIS

Ruptured intervertebral disk?
Tumor of cauda equina?

DR. MICHELSEN'S DIAGNOSIS

Neurofibroma of cauda equina?
Ependymoma of cauda equina?

ANATOMICAL DIAGNOSIS

Neurofibroma of cauda equina.

PATHOLOGICAL DISCUSSION

DR. KUBIK: Dr. W. J. Mixter operated on this patient. He started out by taking off the lamina of the fourth vertebra and came down on a tumor beneath the dura. The tumor, which was found to extend from the lower margin of the lamina of the second lumbar vertebra to the upper margin of the lamina of the fifth lumbar vertebra, was removed except for small bits that were adherent to one or two of the spinal nerves of the cauda equina. Histologically it was a neurofibroma.

The patient made a good recovery, but still has some pain. It is rather interesting, considering the large size of the tumor, that the abnormal neurologic findings were not pronounced, but this is not unusual. We have had cases of both neurofibroma and ependymoma in that locality with no abnormal neurologic findings.

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The Journal does not hold itself responsible for statements made by any contributor.

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UNITED WAR FUND

Now in full swing, the Greater Boston United War Fund campaign reflects the will of a great community working together for the common good. Before Thanksgiving Eve, $7,650,000 must be raised to meet the 1945 needs of home-front and fighting-front services.

Year in and year out, services here at home are adding new and tangible meaning to the words, "Life, Liberty and the Pursuit of Happiness." Throughout the world, the war services are giving convincing proof of their worth. United Nations Relief provides food, shelter and medical supplies to sixteen allied countries — Belgium, Great Britain, Czechoslovakia, Denmark, France Luxembourg, Greece, Italy, Lithuania, Norway, Holland, the Philippines, Poland, Russia, China and Yugoslavia. Refugee Relief Trustees helps refugees of war-torn countries until they become integrated and contributing members of a free society. The United States Committee for the Care of European Children brings youngsters to this country from ravaged countries and undertakes their care while they are here.

"Show That You Care" is this year's campaign cry. Physicians have always cared, serving rich and poor alike. And they, because they are physicians, understand better than others the harmful results of malnutrition in occupied countries and the deteriorating effect of the war prisoner's life. Knowing so well what is at stake, they should give generously and wear their Red Feathers with pride.

THE CONTROL OF CROSS INFECTIONS IN HOSPITALS

The modern treatment of many severe diseases often requires elaborate methods of diagnosis and many forms of therapy, which are difficult to carry out in the home. Most hospitals are provided with the necessary facilities and with properly trained personnel for these diagnostic and therapeutic measures. The fact, however, that many people sick with various infectious diseases are brought together in the same wards and buildings carries with it the risk that patients will acquire infections that they did not have on admission and that they would not have acquired if treated at home. The greatest risk of cross infection is, of course, in infants' and children's wards, where sources of infection are always present. With adults, there is considerable risk for those with wounds and burns and for women in the puerperium.

The last decade has seen great advances in the study of such infections. The ability to identify specific types of pneumococci and streptococci has made possible the tracing of cross infections due to these organisms. More recently, extensive studies have been carried out, particularly in Great Britain

and in this country, on methods for controlling such infections. Particular attention has been paid to air-borne infections and their control with the use of ultraviolet light and germicidal aerosols.

In 1939, the Preventive Medicine Committee of the Medical Research Council of Great Britain appointed the Subcommittee on Cross Infections in Hospital Wards. This committee* has just published an abbreviated report that contains practical suggestions for civilian hospitals in wartime Britain. It may well serve as a guide for use in hospitals everywhere, as well as for the planning of improvements in hospitals or in the construction of new hospitals during the postwar period.

In a foreword to this report, Sir W. Wilson Jameson, the British Minister of Health, points out the great and steady drain that cross infections make on hospital finances and efficiency. Overhead expenses continue and admissions are delayed while the wards are kept in quarantine. Patients who are detained on account of intercurrent diseases may even die and are, in any case, a continuing source of expense and anxiety. For these reasons, requests for improvements and equipment calculated to lessen the risk of such infections should receive careful attention. When new construction is contemplated, the prevention of cross infection should be an over-riding consideration, and expert advice should be sought.

The report outlines in adequate detail the sources and modes of infection, and indicates in a practical way how these actually come about in practice. Particular attention is called to the great increase in bacterial counts in the air of hospital wards during sweeping and bedmaking. The methods of preventing and controlling cross infection are given in considerable detail, including general administrative procedures, those for admitting patients and methods of isolation nursing. The problem of chemoprophylaxis is considered. The role of ward visitors and ways of minimizing infection from this source, as well as from the medical and hospital personnel, are given appropriate attention.

Many forms of labor-saving devices are mentioned. Simple methods for the control of contact and mediate infection are enumerated. These include washing of the hands, care of laundry, preparation of food, proper care in taking temperatures and in the handling of children's playthings and a technic for surgical dressings. The problem of controlling droplet-borne and dust-borne infections is also considered from the point of view of ventilation, bed spacing and the use of face masks and aerial disinfectants. Methods are outlined for the treatment of bedclothes and that of ward floors with spindle oil or another suitable oil in such a manner as to reduce or to eliminate dust.

An entire section is devoted to the procedures to follow on the occurrence of cross infection in a ward. Detailed methods are given for discovering the source and the mode of spread, attention being given to individual diseases, such as hemolytic streptococcus infections, measles, enteric infections, chicken pox and gonococcal vulvovaginitis.

At the end of the memorandum is an appendix containing an outline of details concerning disinfection and sterilization. A second appendix gives practical rules for isolation nursing in cubicles or on open wards. Others outline special precautions for maternity units, rules for ward dressing teams and methods of applying dust-preventing oils. Finally, there is an appendix outlining a course of practical bacteriology for nurses, with suggestions for demonstrations and practical work for the instruction of all interested personnel in the part they must play in preventing cross infection.

All the subject matter outlined is contained in twenty-eight pages of text. Every physician and administrator who is responsible for the care of hospitalized patients can readily profit by reading and studying this brief memorandum. The details are also well adapted for use in the teaching of nurses in training schools. Furthermore, graduate nurses who are responsible for the care of patients in hospitals will profit by acquainting themselves with the contents of this memorandum.

*_The Control of Cross Infection in Hospitals._ Memorandum prepared for the Committee on Preventive Medicine of the Medical Research Council by the Sub-Committee on Cross Infections in Hospital Wards. Medical Research Council, War Memo. No. 11, 34 pp. London: His Majesty's Stationery Office, 1944.

OBITUARY

WILLIAM BRADLEY BREED

1893–1944

"When a man becomes dear to me,
I have touched the goal of fortune."

William Bradley Breed was born in Syracuse, New York, the younger son of a physician. He lost his father when a child, and after the death of the brother, his mother took him to Germany for a year, where he continued his education and studied the violin. He later graduated from the Hackley School in Tarrytown-on-the-Hudson. When he entered Harvard College in 1911, his mother established herself in Cambridge, remaining there until her death, while he was still an undergraduate.

Backrack

WILLIAM BRADLEY BREED

During his college years he continued to show an interest in music; he was a member of the University Musical Clubs and leader of the University Mandolin Club. He had membershipalsoin Delta Upsilon, the Speakers' Club and the Deutscher Verein. At the Harvard Medical School, from which he graduated with the class of 1919, he was a member of the Boylston Medical Society, Phi Rho Sigma, the Aesculapian Club and the Stork Club.

In 1918 and 1919 Doctor Breed served as medical intern in the Massachusetts General Hospital; the following year he held a residency at the New England Deaconess Hospital, later establishing himself in the practice of internal medicine in Boston.

He was married in 1925 to Ruth Williams, of Dedham, who survives him, with their three children, Elizabeth, Sylvia and William.

The posts that he occupied and the positions of trust that he held are ample evidence of the esteem in which he was held by his professional colleagues. For the greater part of his active medical career he was on the staff of the Massachusetts General Hospital, receiving his final appointment as physician in 1936, the same year in which he became a member of the General Executive Committee. In that year, also, he was appointed associate in medicine at the Harvard Medical School.

From 1925 until 1936 he was visiting physician to the House of the Good Samaritan, joining its honorary staff in the latter year. He was physician to St. Luke's Home and a member of the courtesy staff of the New England Baptist, the New England Deaconess, the Faulkner and the Robert Breck Brigham hospitals. He became an associate editor of the *Journal*, then the *Boston Medical and Surgical Journal*, in 1923, retiring to the less active editorial board in 1937. In 1942 he was appointed to the Committee on Publications of the Massachusetts Medical Society.

For a number of years Doctor Breed was a member of the Council of the Society, and in 1943 and 1944 he served as chairman of the War Participation Committee. He was a member of the New England Heart Association, the American Clinical and Climatological Society and the American College of Physicians. In the American College of Physicians he had been governor for Massachusetts since 1935 and chairman of the Board of Governors since 1942, also being a member of the Committee on Credentials and a member *ex officio* of the Board of Regents.

His published articles appeared in the *Boston Medical and Surgical Journal*, the *New England Journal of Medicine* and the *Annals of Internal Medicine*.

Such a list of positions held and of varied contributions to medical progress, however outstanding

as it is, does not begin to indicate the real reasons for Doctor Breed's conspicuous success in the practice of medicine and in the art of living. His sincere and unflagging interest in people, his patient understanding and his gift for friendship are attested to by a host of devoted patients and friends — these can hardly be separated, since so many of his patients became his friends, and so many of his friends were his patients. As the late Professor Hans Zinsser wrote of him in the autobiography *As I Remember Him*, ". . . [he] was one of those precious individuals whom nature had meant to be physicians."

Certain significant factors in his life cannot be dissociated from his complete personality: his devotion to his home and family, after those years when he had had so little of either; his love of music — he was once rated by Philip Hale as the best amateur violinist in Boston; and his interest in fishing — he was a lover of little rivers and of pools and ripples.

Let this be taken as a tribute to his particular genius, that to his friends he is still a present, vibrant reality, to be found at the Tavern Club with his violin, or encountered in the corridors of the Massachusetts General Hospital, or met upon a rocky beach of Moosehead Lake. If remembrance is some part of immortality, then that part of immortality is assured.

"They have not gone, nor can they dwell apart
Who still hold place within some human heart."

J. G.

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

BLAISDELL — J. Harper Blaisdell, M.D., of Winchester, died October 25. He was in his fifty-ninth year.

Dr. Blaisdell received his degree from Harvard Medical School in 1911. He limited his practice to dermatology and taught for many years at the Harvard Medical School. He was a member of the staffs of the Massachusetts General Hospital and the Boston Dispensary and served as consulting dermatologist for several other hospitals. He was a member of the American Medical Association, the American Dermatological Association and the Atlantic Dermatological Conference. He was past president of the New England Dermatological Society and, at one time, chairman of the Section of Dermatology and Syphilis of the American Medical Association. He had long been prominent in the affairs of the Massachusetts Medical Society, and was one of the prime movers in the organization and administration of the Blue Cross and the Blue Shield.

His widow and two sons survive.

CHRISTIERNIN — Charles L. Christiernin, M.D., of Maplewood, New Jersey, died October 18. He was in his sixty-seventh year.

Dr. Christiernin received his degree from Harvard Medical School in 1906. At the time of his death he was medical director of the Metropolitan Life Insurance Company of New York. He was active in the medical societies of the United States and Canada, and was well and favorably known in both life-insurance and health circles in the two countries. He had served as treasurer, vice-president and president and as a member of the Executive Committee of the Association of Life Insurance Medical Directors. He was a member of the American Medical Association.

His widow and a son survive.

FENWICK — George B. Fenwick, M.D., of Chelsea, died October 27. He was in his sixty-eighth year.

Dr. Fenwick received his degree from Harvard Medical School in 1904. He was a member of the local Selective Service board and had organized the medical unit of the Massachusetts Committee on Public Safety in Chelsea.

His widow, a daughter and a son survive.

MARSHALL — Commander John R. Marshall (MC), U.S.N.R., of Somerville, died October 14 at the United States Naval Hospital at Shoemaker, California, where he was stationed as a surgeon. He was in his fifty-seventh year.

Dr. Marshall received his degree from Harvard Medical School in 1918. He was a staff member of the Cambridge Hospital, the Symmes Arlington Hospital and the Lawrence Memorial Hospital and had formerly served at the Mayo Clinic. He was a member of the American Medical Association and a fellow of the American College of Surgeons.

His widow, a daughter and two sons survive.

SHAW — Albert J. Shaw, M.D., of Newton, died May 23. He was in his seventy-third year.

Dr. Shaw received his degree from Harvard Medical School in 1894. He was a member of the American Medical Association.

His widow survives.

SIMS — Frederick R. Sims, M.D., of Northampton, died October 26. He was in his sixty-sixth year.

Dr. Sims received his degree from Harvard Medical School in 1902. He served in the state hospitals at Danvers and at Taunton before going overseas as a major in the Medical Corps in World War I. He was chief medical officer at the Bedford Veterans Hospital from 1934 to 1937. At the time of his death he was psychiatrist and retired chief medical officer of the United States Veterans Administration Facility in Northampton. He was a member of the New England and the American psychiatric societies.

His widow, a son, a brother and a sister survive.

CORRESPONDENCE

DEPRIVATION OF LICENSES

To the Editor: At a meeting of the Board of Registration in Medicine held October 18, the Board voted to revoke the license of Dr. Robert E. Conlin, 18 Auburn Street, Woburn, to practice medicine because of gross misconduct in the practice of his profession as shown by his conviction in court and treatment of a patient.

H. Quimby Gallupe, M.D., *Secretary*
Board of Registration in Medicine
State House
Boston

To the Editor: At a meeting of the Board of Registration in Medicine held October 18, the Board voted to revoke the license of Dr. Morris J. Kupper, 961 Blue Hill Avenue, Roxbury, to practice medicine because of gross misconduct in the practice of his profession as shown by collusion.

H. Quimby Gallupe, M.D., *Secretary*
Board of Registration in Medicine
State House
Boston

TRANSFUSION ACCIDENTS

To the Editor: In the December 8, 1938, issue of the *Journal* you were kind enough to publish my letter concerning a series of severe transfusion accidents in all of which the patients had died following the administration of incompatible blood. Since then, it has been my misfortune to have seen an increasing number of similar cases. Although I have often commented on them both in writing and at lectures, it seems wise at this time to make the following suggestions:

Give whole blood only if it is *urgently* indicated, and not simply as a "boost" or because it is readily available from a blood bank. Too many transfusions, particularly now that blood banks have been established in a large number of hospitals, are being given as a more or less routine measure in surgical operations. Indications for the use of whole blood are relatively few.

If, after due consideration, it is believed that whole blood and not plasma or fluids should be given, it is imperative:

To type both the patient and the donor with high-titer serums.

To retype banked donor blood before use even if it has already been labeled.

To cross match the donor's cells with the recipient's serum. This should be done by the Landsteiner–Levine test-tube technic, the slide cross-matching technic often being unreliable.

To have the results of the cross match checked either by an experienced technician or by an experienced physician. Reliance on inexperienced personnel for something as inherently important as a blood-grouping test may, and often does, result tragically. Unfortunately it appears to be a frequent practice to entrust blood-typing and cross-matching procedures to the lowliest intern or the newest technician.

If the above procedures have been carried out the transfusion may be started. During administration of the first 50 to 100 cc., the patient should be carefully observed by an experienced observer. Any complaint of pain in the flanks, of a sense of constriction in the chest or even of a "queer" feeling should be carefully heeded and the transfusion should be immediately stopped. This requires a wide-awake patient who can feel pain and other sensations and precludes the use of transfusions during both general and spinal anesthesia. If the first 50 to 100 cc. of blood go in without reaction, it is reasonably safe to assume that the blood is compatible and that the cross match has been satisfactorily performed. *This in vivo test is of utmost importance and should never be ignored.* It is often lifesaving, since the recipient can take perhaps up to 100 cc. of incompatible blood without too much difficulty, whereas more than that amount results in an irreversible agglutination of red cells within the circulation and the renal glomeruli and in the deposition of hematin plugs within the tubules. The end-results of such a severe reaction — aside from hemoglobinuria and hemolytic anemia — are renal failure, azotemia and almost always death. No amount of fluids, alkalies, hypertonic solutions and so forth can modify this essentially mechanical nephropathy, in which the glomeruli and tubules are largely blocked and functionless.

If the patient is pregnant or has been delivered, or if more than one transfusion is contemplated, an Rh determination should be performed in addition to the regular blood-grouping tests. If good anti-Rh testing serum is not available, an exceedingly careful cross match (test-tube technic) should be performed, and the in vivo reaction carefully watched.

As I have repeatedly stated, these severe transfusion reactions of incompatibility are by no means scarce. I have seen many of them, but few are reported. Their essential tragedy becomes greatly enhanced when it is realized, too late, that the transfusion was not essential and could well have been omitted.

The following conclusions may be made:

Too many transfusions of whole blood are being given, often without sufficient indication.

Typing and cross-matching procedures should at least be checked, if not completely performed, by thoroughly trained and competent personnel, using the best available methods.

Whole blood should not be given to a patient while under the influence of a general or spinal anesthetic.

The patient should be carefully watched during the administration of the first 50 to 100 cc. of blood, and the transfusion should be immediately discontinued in the presence of a reaction, however slight.

The severe transfusion reaction is best treated by its prevention.

Prevention may be facilitated by standardization of technic, methods of administration and so forth. This might well be placed under the purview of a committee of the Massachusetts Medical Society.

WILLIAM DAMESHEK, M.D.

113 Bay State Road
Boston 15

NOTICES

HARVARD MEDICAL SOCIETY

It has been decided to renew the meetings of the Harvard Medical Society, which were discontinued at the beginning of the war. The first meeting will be held at 8:15 p.m., November 14, in the Amphitheater of the Peter Bent Brigham Hospital. Subsequent meetings are scheduled for the second Tuesday evening of each month. Each meeting will open with the presentation of a clinical case with discussion, followed by three papers of fifteen minutes' duration each and a five-minute discussion of each paper. Arrangements have been made for the publication of reports of these meetings in the *Journal*.

Under this plan it will be possible to present clinical studies as well as the results of fundamental investigation. This should afford an opportunity for the student body, the faculty and the interested medical profession to keep in touch with the many studies now being carried on in the different departments of the Harvard Medical School and its associated teaching hospitals.

NEW ENGLAND OPHTHALMOLOGICAL SOCIETY

A meeting of the New England Ophthalmological Society will be held at the Massachusetts Eye and Ear Infirmary, 243 Charles Street, Boston, on Tuesday, November 21, at 8 p.m.

Following the business meeting, Miss Anita B. Mangiaracine will speak on the topic "Bacteriological Observations." A symposium "Some Nonsyphilitic Interstitial Lesions of the Cornea" will then be presented by Drs. Covitz, Verhoeff, Lahey and Cogan. This will be followed by a paper "Preliminary Report on Bilateral Surgery in Alternating Strabismus" by Drs. Lemoin and Moore, and Miss Alice Scott.

SUFFOLK DISTRICT MEDICAL SOCIETY

The fall dinner of the Suffolk District Medical Society will be held on Saturday, November 18, at the Harvard Club of Boston, 374 Commonwealth Avenue, Boston. A social hour beginning at 6:00 p.m. will be followed by dinner in Harvard Hall at 7:15. His Excellency, Leverett Saltonstall, will speak on the topic, "Medical Social Security," and Dr. Roger I. Lee on "Health Insurance?"

It is urged that doctors bring their wives and particularly that the wives of all doctors absent in the service, whether or not the doctor is a member of Suffolk Society, be invited by members as their guests. Each member who sends to the treasurer with his own application the names of such service wives will receive free tickets for them. The tickets, $3.00 each, must be purchased in advance by sending cash or a check to the treasurer, Dr. Richard S. Eustis, 319 Longwood Avenue, Boston 15. Other members of the Massachusetts Medical Society may apply after November 8.

UROLOGY AWARD

The American Urological Association offers an annual award "not to exceed $500" for an essay (or essays) on the result of some specific clinical or laboratory research in urology. The amount of the prize is based on the merits of the work presented, and if the Committee on Scientific Research deem none of the offerings worthy, no award will be made. Competitors shall be limited to residents in urology in recognized hospitals and to urologists who have been in such specific practice for not more than five years. All interested should write to the secretary for full particulars.

The selected essay (or essays) will appear on the program of the forthcoming June meeting of the American Urological Association.

Essays must be in the hands of the secretary, Dr. Thomas D. Moore, 899 Madison Avenue, Memphis, Tennessee, on or before March 15, 1945.

(*Notices continued on page xii*)